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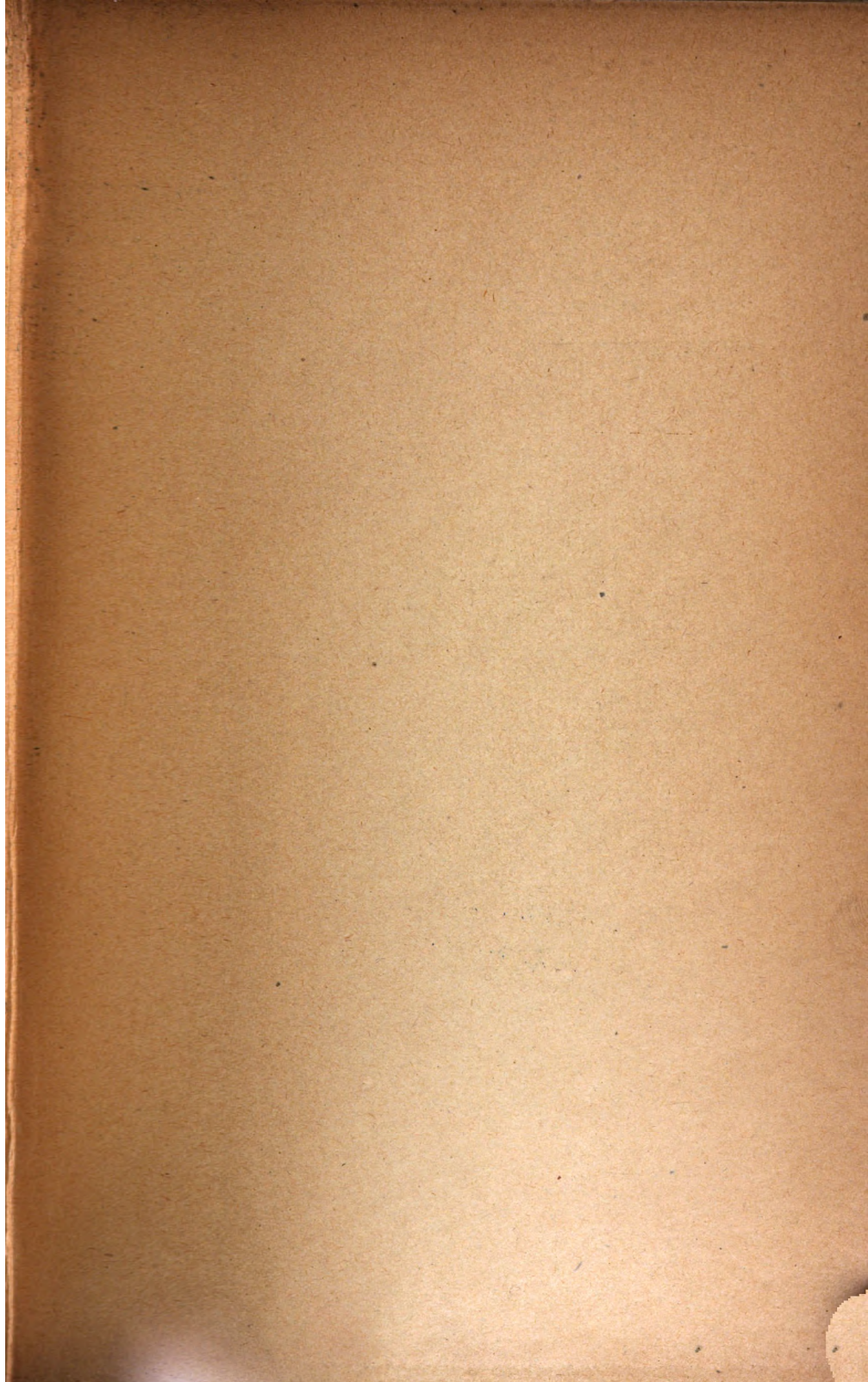


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London

GUY'S HOSPITAL REPORTS.

EDITED BY

F. J. STEWARD, M.S.

AND

HERBERT FRENCH, M.D.,

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THE CHRONIC RELAPSING PYREXIA OF HODGKIN'S DISEASE.

BY FREDERICK TAYLOR, M.D.

It has long been known and taught, not only that Hodgkin's disease might be accompanied by pyrexia, but that the pyrexia might occur in numerous short attacks separated by periods in which fever was absent.

This was prominently brought forward by Sir William Gowers in his article in Sir Russell Reynolds' *System of Medicine*, based on one hundred and fourteen recorded cases.¹

Under the head of temperature he states that "of forty cases in which the presence or absence of pyrexia was carefully noted, it was absent, or present only during some final intercurrent inflammation, in thirteen cases, while twenty-seven cases presented elevation of temperature as part of the special disease."

He says that pyrexia is more frequent in cases occurring under twenty years of age; that it is variable and commonly irregular; and that three types may be recognised. In one the temperature is continuously raised with slight diurnal variations of a degree or a degree and a half. "A second type is characterised by periods of pyrexia in which for several days a high temperature is maintained, the daily variation being slight. Alternating with these pyrexial periods are intervals of several days in which the temperature is normal or nearly so." A third type, he says, is

¹ *A System of Medicine*, edited by J. Russell Reynolds, vol. v., 1879. Art. Hodgkin's Disease, p. 336.

"characterised by morning remissions, the temperature being always higher in the evening than in the morning," and the daily variations are from one to three degrees.

But the same case may present two or more types of pyrexia.

Of subsequent writers in English text books many appear to have relied upon this description, and no material addition has been made to it. Nor, indeed, has much been added by way of confirmation. Fagge in his first edition² quoted Gowers, and Dr. George R. Murray, of Newcastle, in Prof. Allbutt's *System of Medicine*, does the same in more detail.³

But the relation of high temperature to enlargement of the glands, whether in the form of Hodgkin's disease, or in the form of a lymphatic leucæmia, had been often observed; and the remission and relapses of fever, which form Sir William Gowers' second variety, and to which I wish especially to call attention, had excited remark.

I remember that on the occasion of my showing, in 1873, a case of combined lymphatic and splenic leucocythæmia at the Pathological Society,⁴ the late Sir William Jenner, who was presiding, remarked upon the occurrence of pyrexia in allied cases, and upon the fact that exacerbations of pyrexia coincided with increase in the size of the glands, and falls of temperature with subsidence of the glands. And at the Clinical Society, in 1876, two cases of Hodgkin's disease were recorded by Sir William Gowers and Dr. Greenfield respectively,⁵ in which it is clear that relapses or recurrences of temperature took place, though details are not given. Dr. Greenfield, however, called attention to the subject in his remarks. Probably the former, if not the latter, of these cases was known to Sir William Gowers at the time his article was written.

² *The Principles and Practice of Medicine.* By C. Hilton Fagge, vol. ii., 1886, p. 336.

³ *A System of Medicine*, Allbutt, vol. v., 1897, p. 580.

⁴ *Path. Trans.*, vol. xxiv., 1874.

⁵ *Clin. Soc. Trans.*, vol. x., 1877, p. 33. A Case of Lymphatic Leucocythæmia treated with Phosphorus. By W. R. Gowers, M.D. *Idem*, p. 43. A Case of Hodgkin's Disease with increase in the number of white blood-corpuscles, treated with phosphorus. By W. S. Greenfield, M.D.

In 1879, I had under my care at the Evelina Hospital for Sick Children, a case of Hodgkin's disease, an account of which I read before the Pathological Society in November of that year.⁶ In this case there was no leucocytosis, and the temperature record during the last four months of life showed five periods of pyrexia varying from seven to thirty days in duration, with four intervals of apyrexia, relative or absolute, varying from six to seventeen days in duration. I think I may safely say that I had then no knowledge of Gowers' description of the course of temperature in this disease. It may save some trouble if I extract from the Pathological Society's Transactions⁷ the account I then gave of the temperature.

"The temperature during his illness fluctuated considerably. On May 7th, two days after admission, it rose nearly to 104°, continued about 103° till the 10th, then fell during four days to 98°; continued normal till the end of May, rose suddenly in the first days of June to 103°, and fell remittingly till the 10th, continuing to be 98° in the morning and 100° in the evening until the 20th. From this date till July 18th it formed a curve reaching 103° at its summit, June 29th to July 8th, with but little difference between morning and evening records. For a few days the temperature was normal, then formed another curve, beginning July 24th, reaching 102°—103·5° between July 28th and August 9th, and falling to 100° on August 15th. From this until the 30th it was scarcely above the normal; it then again rose, reaching its highest, 103·6°, on September 18th, and gradually fell till death. A certain amount of correspondence was observed between the condition of the glands and the variations of the temperature. Thus the glands were painful on admission when the temperature was high, and less painful during the remission of May. They were noticed to be larger during the elevation of June 20th to July 18th. They were again noticed to be 'not so large,' and to seem smaller on August 27th after twelve days' normal temperature, and they were swollen and tender after ten days, during which the temperature had been rising. There was no leucocythæmia.'

⁶ Path. Soc. Trans., vol. xxxi., 1880, p. 282.

⁷ Loc. cit., p. 284.

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I have searched in the old case books in vain to find the chart, but the pyrexial periods and intervals may be thus tabulated :—

Pyrexia	...	7 days.			
Interval	17 days.
Pyrexia	...	10 "			
Interval	10 "
Pyrexia	...	30 "			
Interval	6 "
Pyrexia	...	22 "			
Interval	15 "
Pyrexia	...	30 "			

American physicians have long been made acquainted with these cases. Professor Osler wrote the article on Hodgkin's Disease in Pepper's *System of Practical Medicine*⁸; he describes the recurrent temperature and mentions Gowers' article.

Again in Pepper's text book of the *Theory and Practice of Medicine*,⁹ Professor Osler describes the occurrence and alludes to a case having occurred under his own care.

Dr. J. H. Musser, of Philadelphia, has written an article especially devoted to this subject.¹⁰ He kindly sent me a reprint of it, and I am indebted to it for several references. He recalls Murchison's case which was read before the Pathological Society¹¹ as well as Gowers' article, and gives abstracts of cases published in Germany by Pel, Ebstein, Hanser, Völckers, and others. He concludes by reporting two cases of his own which were, no doubt, instances of Hodgkin's disease, although in neither was a post-mortem examination obtained.

Ebstein's case¹² is of considerable importance, because it was described as a case of "Chronic Relapsing Fever, a new infectious disease." When the whole case is before us it obviously does not materially differ from cases of Hodgkin's disease with relapsing pyrexia which have been published before and since.

⁸ Vol. iii., p. 885.

⁹ Vol. ii., 1894.

¹⁰ Transactions of the Association of American Physicians, 1901. Notes on the fever of Hodgkin's disease, recurrent (Rückfall) fever, Ebstein's disease.

¹¹ Path. Trans., vol. xxi., 1870, p. 372.

¹² Berliner Klinische Wochenschrift, 1887, vol. xxiv., pp. 565 and 837.

But Ebstein's first communication was made when the patient was still alive ; the record of temperature covers two hundred and thirty-eight days, or nearly eight months, during which occurred nine attacks of pyrexia of thirteen to fourteen days' duration, with intervals of from ten to eleven days, while a tenth attack was still in progress. The spleen was enlarged, but there was no enlargement of the external lymphatic glands, no clinical evidence of enlargement of the internal lymphatic glands, no morbid appearance of the blood, and no obvious disease of any internal organ.

Though aware of Murchison's case and Gowers' article, Ebstein associated the repeated febrile attacks with the enlarged spleen, and concluded that he had a new infectious disease—a relapsing fever of chronic form which differed from relapsing fever, Rückfallsfieber, febris recurrens, or Rückfallstypus, in the persistent repetition of the attacks, and in the absence of the spirillum from the blood. And the term "Ebstein's disease" has even been used to describe this chronic relapsing condition.

But after a long eleventh attack and a short twelfth the patient died exhausted. And in a second article, three months after the first, Ebstein described the autopsy, at which was found enlargement of the bronchial, mediastinal, and mesenteric lymph glands, with very numerous nodules of lymphoid appearance in the lungs, liver, kidneys, and spleen.

The pathological reading of the case was then obviously Hodgkin's disease, and it differed only from the supposed typical forms of that disease in the freedom of the external glands, a condition now well known to occur, and in the particular form of pyrexia, with which at that time the profession was little familiar.

I need not give details of the other German cases to which I have referred. Musser's article gives excellent abstracts of several of them, and I will only say that Pel's first case was published two years before Ebstein's, and that his others appeared in the same journal in the interval shortly before Ebstein's second article. The differences between the cases up

to that date only showed, if I may put it so paradoxically, that the cases could not be separated from one another.

It might be thought that if all these cases were published, and their significance was discussed nearly twenty years ago, it is of little use either to fight the battles over again at the present time, or to weary my readers by the publication of cases which may only be repetitions of those already known. But on the one hand, I have reason to believe that the profession is not widely familiar even with occurrence of this relapsing fever in Hodgkin's disease, much less with its extraordinary duration and persistence; and, on the other hand, I wish to call attention to the great value which a knowledge of its characters may have for the diagnosis of such obscure cases as that which Ebstein reported, and of some which I shall myself here record.

Of the different types of pyrexia—continuous, remittent, intermittent, and relapsing—the relapsing form is the most interesting because most rare; and its occurrence when it is recognised will obviously have more diagnostic value than the other forms. These other forms are common to many prolonged and chronic infections, for instance, tubercle, infective endocarditis, typhoid fever, pyæmia, bronchopneumonia, cirrhosis of the liver; and when such a pyrexia lasts a long time without any marked or distinctive physical signs, the diagnosis is often difficult. Experience of this kind is of daily occurrence in cases which may prove subsequently to be acute tuberculosis, typhoid fever, malignant endocarditis, suppurative pylephlebitis, or pyæmia from almost any source. But if more or less complete relapses of pyrexia take place, with definite intervals of some days in which the temperature is normal or even subnormal, there are really few conditions to which such manifestations can with confidence be attributed.

In spite of the name which Ebstein gave to the phenomena—chronic relapsing fever—there should be no difficulty in distinguishing even the first or second attack from the pyrexia of “relapsing fever” or spirillum fever. For in the former case, as may be seen from the charts of Ebstein's and Pel's cases, and from the charts of cases here published, the febrile attacks

terminate always by *lysis*, even if somewhat rapidly, and the acme is removed by three or more days from the first subnormal temperature of the interval; whereas in spirillum fever, one of the most remarkable features is the termination of the febrile period in a rapid rise of temperature to 106°, 107°, or even 108°, and the sudden fall by *crisis*, in twelve to fifteen hours, to a point often far below the normal. The occurrence of a fourth or fifth fever of equal duration and severity with the first almost certainly excludes spirillum fever; a duration of ten, eleven, or more days is uncommon in the attacks of the acute specific disease; and an examination of the blood should show the spirillum in the one case, and its absence in the other.

The diagnostic importance of the temperature is well illustrated by one of the early cases, to which reference has been already made, and which presented close resemblances with the case of Ebstein. It is the first of those published by Pel, of Amsterdam.¹³ On June 1st, 1884, the patient, hitherto well, had shivering, fever and nausea, dry cough and pains in the abdomen. He was admitted to hospital on June 7th, and was obviously regarded as a probable typhoid case, though no other signs than an enlarged spleen and bronchitis were present. Tuberculosis and some blood disease were also considered possible, the latter on account of the anæmia and the enlargement of the spleen. The temperature, however, fell on June 11th, rose again after an interval of fifteen days, and in the whole duration of his illness from June 1st to October 6th, the date of his death, there were five periods of pyrexia, and five intervals of apyrexia arranged as follows:—

Pyrexia	...	11 days.			
Interval	15 days.
Pyrexia	...	10 "			
Interval	9 "
Pyrexia	...	16 "			
Interval	16 "
Pyrexia	...	31 "			
Interval	8 "
Pyrexia	...	10 "			
Interval	2 "

¹³ Berliner Klinische Wochenschrift, vol. xxii., 1885, p. 3.

Each pyrexia showed a gradual rise during four or five days to 102°, a fastigium of a few days up to ten or fifteen days and a fall by lysis during three or four days. The details of the apyretic period are not recorded.

In the eighth week, the middle of the third pyrexia, occurred diarrhœa with no distinctive characters, and in September were seen some doubtful spots, which disappeared again. The spleen varied somewhat with the temperature, enlarging with the fevers and subsiding a little in the cooler periods; but no large glands were detected. The *post-mortem* inspection, however, showed much hyperæmia and swelling and firm consistence of the retro-peritoneal, mesenteric and bronchial glands, while the glands in the hilum of the spleen were swollen, red and soft. It is interesting to note that the relapses of fever were attributed to the ingestion of solid food, a fact which was held to support the diagnosis of typhoid fever; but Pel says that the possibility of a disease of the hæmopoietic organs was held in view, on account of the increasing anæmia, the enlargement of the spleen and the long duration of the illness. The moderate leucocytosis in that case would have only justified a diagnosis of pseudo-leukæmia (Hodgkin's disease), and "*in this case*," says Pel, "*the course of the fever was quite unintelligible.*"

Here then the diagnosis was rendered difficult because the disease of the lymphatic glands was confined to those in the interior of the body, and because the occurrence of this particular form of fever in Hodgkin's disease was not familiarly known. The bearing of this upon two of my cases will be obvious, cases in which, it is true, some external glands were enlarged, but in which either the enlarged glands were not sufficiently numerous or widespread to give confidence in the diagnosis; or the occurrence of the fever itself actually helped to suggest a diagnosis of tuberculosis.

In now introducing my own cases I must admit at once that in none of the three has there been a *post-mortem* examination, but in all, at any rate, the illness has terminated in death, and what I submit for consideration is that the character of the pyrexia in each case confirms a diagnosis which might otherwise

be doubtful. Briefly, the difficulties in the diagnosis were the following :—

In the first case, enlarged and hard glands in the neck were regarded by some of the medical attendants as tuberculous, and by others, as lymphadenomatous.

In the second case, some persistent glands in the neck removed by operation, and shown then to be not tuberculous, were followed by a tumour in the abdomen, about which very diverse opinions were held.

In the third case, an illness of two or three years' duration was accompanied by such a very slight and variable enlargement of the external lymph-glands, that it was a very long time before a diagnosis of such a hopeless disease as Hodgkin's could be wisely entertained.

CASE 1.—On September 9th, 1902, I saw a gentleman, æt. 41, from whom I had the following history :—

On April 5th he had an illness of four or five days' duration, which was regarded as influenza. The temperature rose to 103° , and afterwards fell to 94° or 95° . He had with it headache and lumbar pain. After that he had eight separate attacks similar in character; in all there was fever of four or five days' duration, followed by a subnormal temperature. He saw a consultant in the provinces, who sent him to Switzerland. He was there for six weeks, and had four similar attacks. Thus on July 26th, the temperature was 101° ; on the 27th, 101.4° ; on the 28th, 101.4° ; on the 29th, 99° ; then it dropped to 94° ; and in the following week remained at 95° and 96° . On a Sunday soon after this the temperature was 99.4° at noon, there was much pain in the loins, and the evening temperature was 100° ; on the Monday it was 98.8° in the morning, rose to 101.6° at night; Tuesday, 100.8° in the morning, 102° at night, and after this fell to normal. In the intervals of the attacks the temperature was 94° or 95° . He returned to England on September 1st, and had a long attack in the succeeding week. For three years previously he had had enlarged glands on the right side of the neck which were regarded as tuberculous. He was short, rather thin, dark-haired, looking rather younger than his age. There were enlarged

glands on the right side of the neck extending from near the ear to the clavicle, not projecting much, but distinctly hard. A very small gland was perceptible in the right axilla, but none in the groin. In the right iliac fossa was a rounded mass varying from time to time in size, not painful nor tender. The bowels had been open that morning. The spleen could not be felt, nor could the liver. The sternum was nowhere dull. The blood appeared to be normal, there was no excess of leucocytes, the red corpuscles were 4,000,000 in number; no poikilocytes. A differential count of the leucocytes gave: polymorphonuclears 70 per cent., lymphocytes 24 per cent., hyaline 2 per cent., and others, probably hyaline, 4 per cent. He had seen more than one consulting physician, and opinions hovered between tubercle and Hodgkin's disease. I inclined to the latter. A colleague with whom I consulted inclined to the former. We recommended abstention from work, an open air life as far as possible, and arsenic internally if he could take it. However, within a few days he was taken to another physician, who found some swelling in the right tonsil; a throat specialist who was thereupon consulted found some pus in the supratonsillar fossa and removed the upper part of the right tonsil. In spite of this, which took place on or before the 13th, a fresh attack of pyrexia occurred, and in the evening of September 17th his temperature was 101°. On September 18th it was 101·4° in the morning, 101·8° in the evening. On the 19th it was 99·8°, and the glands were swollen, then the temperature gradually fell to 97·6°, 96·8° and 96°. Some little time after this the glands were removed by operation, but erysipelas or other septic change supervened and he was ill for a long time. He ultimately died early in February, 1903, and I heard from the medical man who had brought him to me that there was no doubt that the case was one of Hodgkin's disease.

Three opinions were held with regard to the nature of the glands in this case; that they were tuberculous; that they were enlarged by infection from the nose or the throat; that they were part of Hodgkin's disease. When I saw him I had recently read Dr. Musser's article on the fever of Hodgkin's disease, and I was

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FIG. 1.—ESTHER T., ÆT. 20.

therefore primed with a strong argument on the side of Hodgkin's disease; and, on the other hand, the description of the febrile attacks agreed with nothing that is commonly seen as a result of tubercular or pyogenic infection, a fact which was admitted by more than one of those who regarded the glands as tuberculous.

In the hardness, the glands were extremely suggestive of tubercular infiltrations, but it is well known that the hyperplasia of Hodgkin's disease is accompanied by variable amounts of fibrous tissue, so that the glands may be either soft or hard; and it is interesting to note that in Ebstein's case the lymph gland swellings as well as the nodules in the liver, spleen, and lungs, had "eine derbe und feste consistenz."

The second case is one to which I have already briefly alluded in my Lumleian lectures on Some Disorders of the Spleen.¹⁴

CASE 2.—Esther T., æt. 20, was admitted under my care into Guy's Hospital, December 14th, 1900. She had always been healthy until after the birth of her first child. On November 27th she had some pain in the loins. In February, 1900, she had a blow on the left side of the neck, and from that time it is stated that a lump appeared and grew until her admission to the hospital. This proved to be a mass of enlarged lymphatic glands in the posterior triangle, close to the sterno-mastoid muscle and to the clavicle; it measured two inches from within outwards, and reached one and a half inches above the clavicle. Behind this was a separate oval gland five-eighths of an inch long (See Plate). The patient was rather pallid, and there was a little pyrexia. She was not otherwise ill, and was moderately well nourished. The spleen was not enlarged, nor the liver. A blood count gave 4,400,000 erythrocytes, 8,000 leucocytes. No differential count is recorded. The glands did not increase in size, indeed, they seemed rather smaller, but it was thought wiser to remove them, and in February, 1901, Mr. Symonds operated.

The glands presented a simple hyperplasia and were regarded as a part of Hodgkin's disease. She left the Hospital on

¹⁴ *Some Disorders of the Spleen*, London, 1904, p. 74.

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March 8th, 1901. On July 28th she was kept awake all night by a bearing down pain. On July 30th she noticed a lump in the abdomen which was very painful. She was sick on the 28th, 30th, and 31st, on which last day she was again admitted. She was pale and rather short of breath. There was a small lump under the scar of the operation, and a small gland in each axilla, but none in the groins. In the abdomen was a mass extending from the left costal margin to one inch to the *right* of the umbilicus and one inch below it. It was freely movable from side to side, but moved little with respiration; it had an irregular surface. The splenic dulness began at the upper border of the ninth rib, and the spleen's edge could be felt half an inch below the costal margin, but separate from the tumour. The liver was not enlarged, but the edge could be felt extending over the tumour on deep respiration. The lower edge of the tumour was quite free from the pelvis, and the mass could be pushed forwards from the loin; though spontaneously the seat of pain, it was not tender.

The apex of the left lung was rather flat to percussion, and a few râles were heard on both sides. The heart was normal; the urine contained a trace of albumen.

She was now in the Clinical ward and came under the care of several of my colleagues in succession, and was under my own care for three weeks before her final discharge. Analysis of the stomach contents showed, shortly after admission, .1 per cent. of acidity in terms of hydrochloric acid; and the presence of free acid, whether lactic, or hydrochloric undetermined. The temperature gradually fell to normal during the next three days, and remained subnormal till August 10th.

A blood count gave erythrocytes, 3,750,000; leucocytes, 7,187; hæmoglobin 60 per cent. On August 15th the temperature began to rise, it was 101° on the 18th, above 102° on the 19th, 20th, and 21st, and fell to normal by the 24th, a pyrexial course of nine days' duration, and during this attack of fever she had again pain in the tumour which she had previously lost, and lost again with the cessation of the fever. Remaining free from fever for thirteen days she had another short pyrexia from September 6th to the 12th inclusive, that is, seven days, and again after nine days'

interval a fever from September 22nd to September 30th inclusive, or nine days. On September 28th the blood count was, erythrocytes, 4,900,000; leucocytes, 6,562; and the differential count proved to be normal. On October 1st the tumour was still mobile, two glands could be felt in the neck near the scar, and suspicions of phthisis at the left apex were entertained.

A fresh pyrexia occupied the period October 5th to October 10th inclusive, six days, and another was from October 15th to the 24th inclusive, ten days. On October 10th the count was—

Erythrocytes	3,800,000
Leucocytes	9,900
Hæmoglobin	65 per cent.

The pyrexial attacks were accompanied by pain in the head and down the left leg, both relieved by phenazonum. Much vomiting about this time led to a suggestion that she might have tuberculous meningitis. The fundus oculi gave negative results, and injections of tuberculin one-tenth milligramme, one-seventh

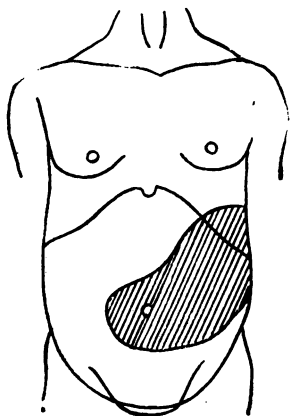
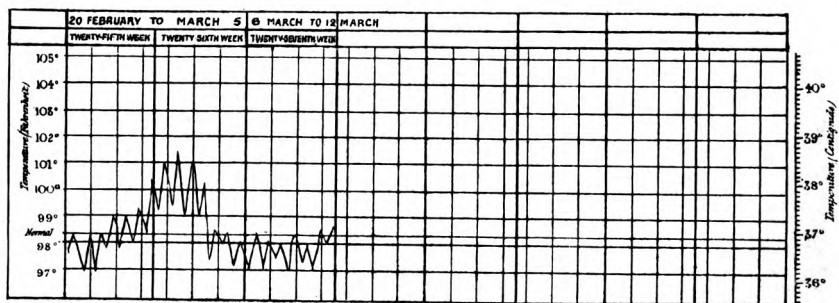
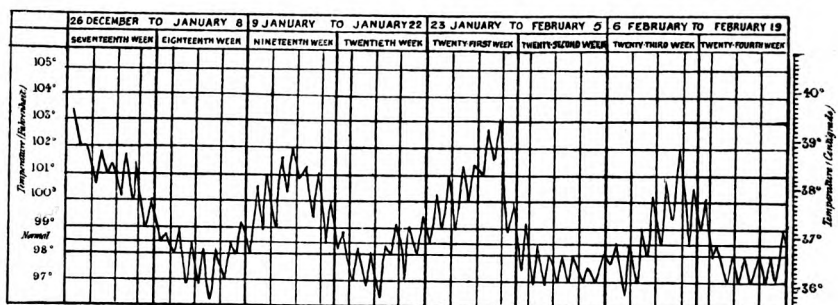
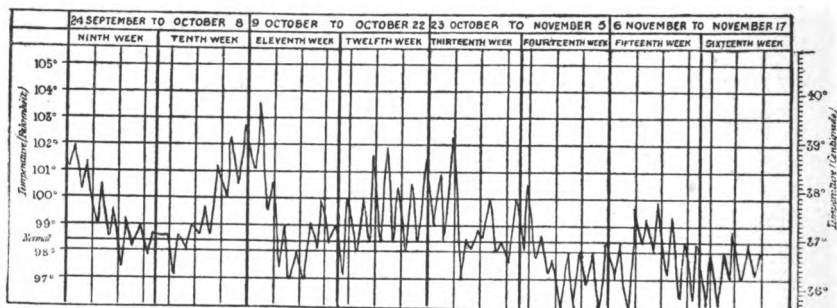
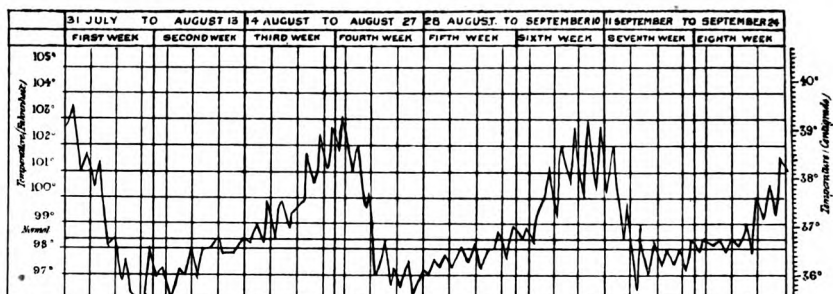


FIG. 2.

The diagram (Fig. 2) shows the position of the tumour on October 11th. The upper border in the middle line was six inches from the ensiform and one and three-quarter inches from the umbilicus; the tumour reached two and a half inches beyond the umbilicus horizontally, and two and a half inches below it in the middle line.

and one milligrammes respectively on the 8th, 12th and 15th November produced no reaction. There was a very slight

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pyrexial curve (No. vii.) from October 27th to November 1st, five days, and one still less (No. viii.) from November 7th to November 10th, equal four days. In the first of these the temperature was not above 101°, in the second not above 100°. She went out November 17th, but was readmitted December 26th. She had been well for three weeks, then pain in the side returned. The mass was now, on January 1st, described as moving with respiration, its anterior margin crossing the middle line one-third of the distance from ensiform to umbilicus (that is, upper third), its edge irregular and indented, coming from the costal margin at the tip of the eighth cartilage, the surface not regular but bossy, the posterior border not filling up the flank, the mass not tender to the touch.

Blood count: Erythrocytes 5,025,000
Leucocytes 9,826

A gland under the old scar was as large as a Spanish chestnut. She remained in until March 12th, and during this time had again the periods of pyrexia precisely in the same way as before. Thus on admission, December 26th, the temperature was 103°; it gradually fell to normal on January 1st, a period of 7 days or more.

(Interval 6 days.)

2nd period.—January 8th to 15th (x.) = 8 days.

(5 days.)

January 21st to 30th (xi.) = 10 days.

(9 days.)

February 9th to 13th (xii.) = 5 days.

(11 days.)

February 25th to March 2nd = 6 days.

Two blood counts were as follows:—

January 21st—Erythrocytes 4,900,000 Leucocytes 12,307

February 16th— " 3,675,000 " 6,458

There was a preponderance of polymorphonuclear cells and no myelocytes. She was discharged on March 12th.

She did not come in again though living close to the hospital, but on enquiries at her home, I found that she died in the early part of 1903, that is nearly two years after the removal of the

glands, or three years from their first appearance after the supposed causative injury.

Very different opinions were expressed by my colleagues as to the nature of the mass in the abdomen. One view was that it had no relation to the glands, but might be renal; another that it was glandular; another, that it was malignant growth another, that it was a tuberculous mass in the omentum. But there were more in favour of its splenic nature, than of any other single possibility.

A note of my own, made in the latter half of February and accompanied by a rough sketch (Fig. 3) is the following:—"The

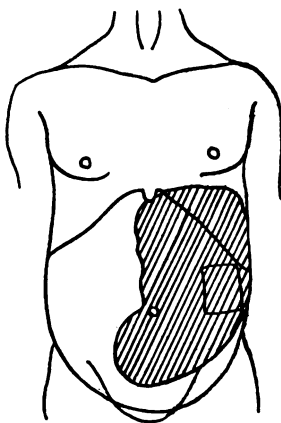


FIG. 3.

tumour is like a spleen, but presents curious differences. It is very broad transversely above. There are many notches of small size, and the whole surface is *bumpy* and undulating, as if the seat of lymphomatous or cancerous masses. The mass does not come down to Poupart's ligament; it is not tender nor painful. Over the square area outlined is a suspicion of resonance on percussion."

Now, if we analyse the temperature we see that between the end of July and the middle of November she had several very definite pyrexial attacks of from seven to ten days' duration, separated by intervals of from eight to twelve days' duration; and from her readmission in December to her discharge, there

were at least four attacks of from five to ten days' duration with intervals of from five to eleven days. This condition of the temperature, to my mind, very strongly supports the view that the case was what we at first thought it was, namely Hodgkin's disease, before the rather anomalous abdominal tumour came in to disturb our calculations. It must be allowed that for a spleen it was somewhat unusual in shape, very irregular on the surface, and much larger than is common in Hodgkin's disease. If it was not the spleen, and we can never know now, it must have been a mass of lymphomatous glands, or perhaps a combination of the two, matted in some way together. The length of time which elapsed between the first appearance of the abdominal tumour and the death of the patient, about twenty months, makes a sarcomatous or carcinomatous growth much less probable.

In my third case the variations in the pyrexial process are not quite so simple as they seem to have been in case 1, and as they certainly were in case 2. It differed chiefly in this, that there were long periods of which no day was entirely free from fever; but in these long periods there were alternations of periods of relatively high fever, with periods of relatively low fever, just as in the other cases, and at other times in this case, there were alternations of periods of pyrexia with periods of apyrexia.

Of this patient I have a complete and continuous record of temperature for twelve months and six days; it ends, however, four months and a half before death took place. During the whole of this twelve months' period, the evidences of Hodgkin's disease consisted only in the slight and variable glandular enlargements, the very moderate enlargement of the spleen, the profuse sweats, and the general malaise and weakness. The temperature was taken always three times, and often four times in the day.

I here give the case in some detail, because in the absence of post-mortem evidence it is desirable that the grounds of the diagnosis should be plain.

CASE 3.—Mr. X., æt. 38, consulted me on September 14th, 1892. Six weeks previously he was waked at 3 a.m. by a pain in the lumbar region which continued off and on with snatches of sleep till 6 o'clock, and then got better and disappeared as he got up. But it recurred, became very severe, and was little influenced by local treatment. After a fortnight he went into the country, lived freely, and the pain left him. Returning to town he suffered from the pain again, and it recurred every day. It began in the middle of the back and worked round to the right side. Except for his statement that he had gout in the feet at the age of 18, he seems to have had no serious illness, and he was usually well, but had occasional fatigue from his business in the City. His appetite was good.

Examination of the heart, lungs, renal region and urine was negative. I raised the question of the position in which he slept, and ordered some salicylate of soda and colchicum with local applications. A month later I heard from his doctor that he was well, and that the modification of his bed, and of his position in bed as I suggested, seemed to have cured him. He was a rather thin man, looking a little worried, and older than his age.

On July 1st, 1893, I saw him again; he had bronchitis five weeks previously and was in bed eight days. He was then told by a doctor that he was in a very weak state, he lost about a stone in weight, was depressed and unfit for work or responsibility, had no inclination for active exercise and was afraid even to cross the road.

His appetite was good and he slept well. In May the glands of the left side of the neck had been enlarged, at first one, then two or three more. I was doubtful about a "click" at the apex of the right lung. After this he went into the country, and in the middle of August he had a recurrence of pain in the back. It was now in the left lumbar region, close down upon the crest of the ilium, never going up to the left shoulder, but sometimes into the left groin, and even into the scrotum. Changes of position failed to relieve it, it came on at night and lasted till 1 or 2 a.m., frequently it appeared suddenly and left again equally suddenly. The urine was always clear, never contained blood, was never thick, and

contained no albumen when I examined him on September 20th. He thought he was weaker and had lost a little flesh. The glands in the neck were much the same as in July, not very large but remarkably hard, several close to the left clavicle, a few smaller ones near the angle of the left jaw, and one or two near the right clavicle. I could not hear anything wrong on this occasion at the right apex. I ordered him some potassium citrate, and belladonna and camphor liniment. He did not take the medicine for long, but about three months later (December, 1893) he had a severe attack, and on the advice of a friend rode for sixteen miles on horseback and got rid of the pain forthwith.

About September 9th, 1894, the pain again recurred in attacks of two or three hours at a time, and he saw me on the 19th. It was variable; at one time between the shoulders, then over the sacrum, right buttock and down the right thigh. At night he could hardly bear the parts to be touched, but in my room he hit himself about freely. The urine was normal. I ordered him potassium iodide, salicylate of soda and antipyrin, in the attacks. But the treatment was ineffectual, the pain constantly occurred, varying in position.

In December, 1895, the pain was in the left flank, near the ilium, passing down into the groin and thigh, generally beginning at 2 a.m., but sometimes in the day time, and lasting two or three hours. *The glands on the left side of the neck have disappeared*, but there are some on the right side, very hard and matted together. He looked quite well. The heart, lungs and urine were normal, and I could find no evidence of disease of the kidney or of any other organ except the cervical glands. In my absence from town Dr. Hale White had seen him and ordered mercury perchloride and potassium iodide. The following day the pain disappeared, but it returned and the medicine was powerless.

In January, 1896, appeared a patch of erythematous redness on the right shin, extending vertically; he could not trace it to a blow, and I could not find any other lesion of the skin, or any scratch or breach of surface. Parts of it were somewhat thicker

and more prominent, as if it might have started in an erythema nodosum. He was not ill and did not seem to be feverish.

He subsequently went to Bath for five weeks. The eruption on the right leg recovered, but recurred as a definite erythema nodosum, and a similar lesion appeared on the left shin. At Bath his temperature was observed to be between 100° and 103° , and he had "dripping perspirations." Malaria was suggested and he took quinine freely under one doctor, who found also that his spleen was enlarged. The lungs were also suspected, but nothing could be found in them. At this time he says that the lumbar pain was often preceded by shivering and followed by sweating.

I saw him on February 29th, 1896, and found a few hard glands in the neck, and the spleen was readily felt on inspiration. He was haggard and had lost six pounds in weight. The temperature for four days had ranged from 98° to 102° , and from this time onwards for twelve months I have the record of his temperatures of which I have spoken; and I shall deal with it in detail at the conclusion of the case. The heavy perspirations continued, often occurring when he slept; and on March 1st and 2nd he had some kind of chill or rigor. He ate fairly, but was weak and unfit for any business or exertion. On March 7th, the heart was healthy, but hypercritical examinations of the apex only elicited an occasional or doubtful râle. The spleen was enlarged as before. On March 16th I could find absolutely nothing wrong with the lungs. He went then to the seaside, where the temperature still continued febrile, the perspirations continued and occasional severe shiverings occurred; but nevertheless he got up and went out. A gland became enlarged in the right groin and subsided again; and the cervical glands of the right side previously enlarged, diminished in size.

On April 13th there were still some large glands on both sides of the neck, especially some under the right sterno-mastoid, and the glands in the right groin, both upper and lower groups, were distinctly large and tender. The lungs were normal. An examination of the blood showed normal quantities of red corpuscles,

leucocytes and hæmoglobin. I ordered him some quinine and arsenic.

During April he had nausea, some sickness, and shivering and sweating. On the 25th I heard by letter, that a gland had appeared above the shoulder blade and again subsided, and that one in the leg was nearly gone. He was taking horse exercise occasionally.

In the first three weeks of May the temperature was very nearly normal, the shiverings were absent and the perspirations were much less. But he had some pain in the right breast and under the arm coming on soon after midnight.

On May 12th he was of good colour, not thinner, could ride an hour without fatigue, but became tired with walking. The spleen was still enlarged, and the glands in the right groin much reduced, but still bigger than those on the left side; those under the right sterno-mastoid muscle were rather large. There was also a gland (or lymph-adenoid tumour) over the right infra-spinatus muscle near the axillary border of the scapula; it was adherent to the muscle or fascia. The blood again appeared to be normal. (I have a note here that he absolutely denies that he ever had syphilis.)

In the last week of May the temperature again rose, the perspirations returned, and he had pains in the chest and in the sacral and iliac regions, but he looked better in the face, was always ready for his meals, and had no cough. He had three tender spots, one at the end of the right costal cartilage, the second below the angle of the right scapula, and the third on the right buttock. The right inguinal glands were certainly smaller than before, the scapular nodule was about the same size, and the right cervical glands were perhaps larger. He was limp, disinclined for work, walked less upright, and slept a good deal in the day. Iron, arsenic and potassium iodide were given. From the middle of June till the middle of July the temperature was again much lower, and during this time he felt better.

In September he appears to have been improving a little, but had had some high fever at times accompanied by perspirations. A large gland had appeared in the right axilla, the spleen was large and the scapular lump was still present. About September

10th he had sharp pain in the right chest near the sternum, followed by a tender swelling on the fifth costal cartilage; and the tenderness of the fourth costal cartilage previously mentioned persisted. Clearly he had some perichondritis. The gland over the scapula was still present, as well as glandular swellings under the angle of the right jaw and at the front of the chin.

In the last week of September and the first fortnight of October the temperature was again very high, and he had perspirations and rigors. On October 12th the perichondritis to the right of the sternum formed a swelling two and a half inches vertically by two horizontally, hard, solid, not fluctuating. The lump over the scapula was much smaller, about the size of a small pea; the glands under the angle of the right jaw were slightly swollen, and the spleen was just perceptible, not descending so far on inspiration as formerly.

He was not more than two pounds lighter than six months ago, had a good colour, felt well when away from work, but found out his weakness if he attempted any business, in the latter half of the day was tired and went early to bed.

During the next fortnight the temperature was higher; he had profuse perspirations, headaches, and nausea. With the severer headaches he had a little wandering. The swelling in the chest increased and subsided and was more painful. I ordered him quinine, arsenic, and strychnine, and elixir of bone marrow.

On December 1st, after a month of varying temperature and correspondingly varying general condition, he was obviously thinner, and weighed only nine stones six pounds. But he had a good colour and good appetite. The perichondrial swelling had had a diameter of four inches, but was now only represented by a little fulness over the fourth costal cartilage. The gland over the scapula was even smaller than it had been two months previously. A gland under the right angle of the jaw was still hard and large, those in the groin were perceptible but not abnormally large. The spleen was as large as it had ever been, and the edge of the liver could now be felt on inspiration coming down to the horizontal umbilical level. Above each clavicle there were some loud expiration, and a whisper was loudly transmitted

equally on the two sides; but he had no cough, no dyspnoea, and expectorated nothing.

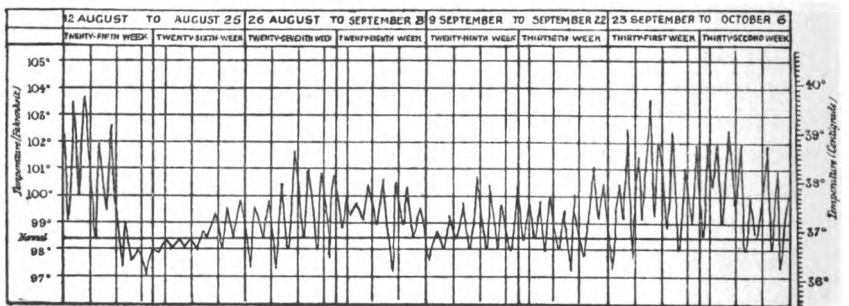
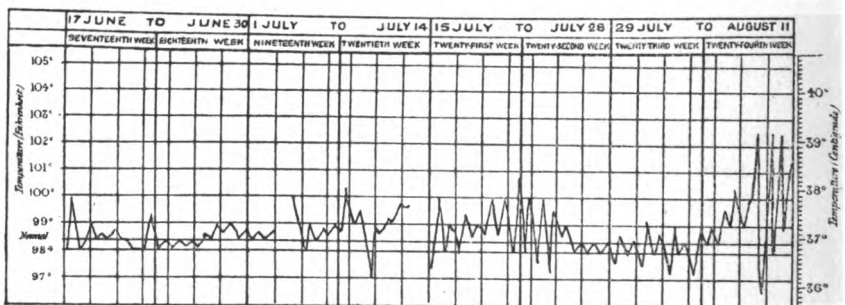
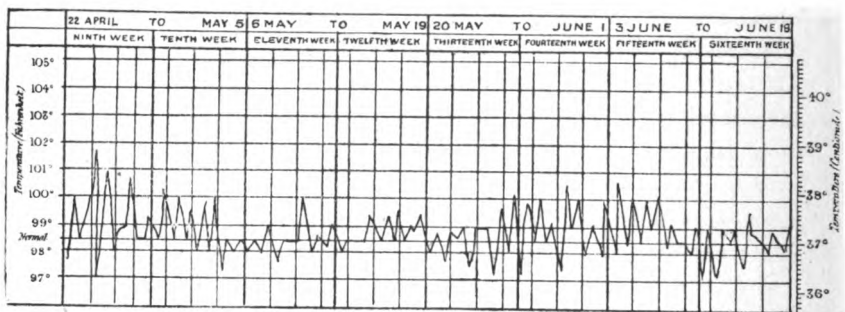
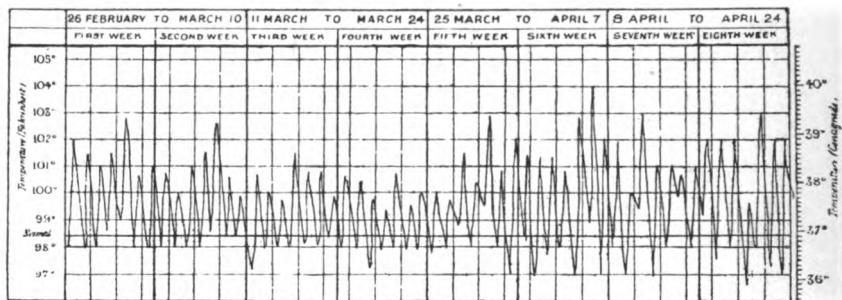
Early in January, 1897, he had pain in the right arm and down the right side, and epigastrium; and later in the right lower chest. A doctor found some fluid on exploration, but did not aspirate. A gland appeared at the lower end of the sternum and disappeared.

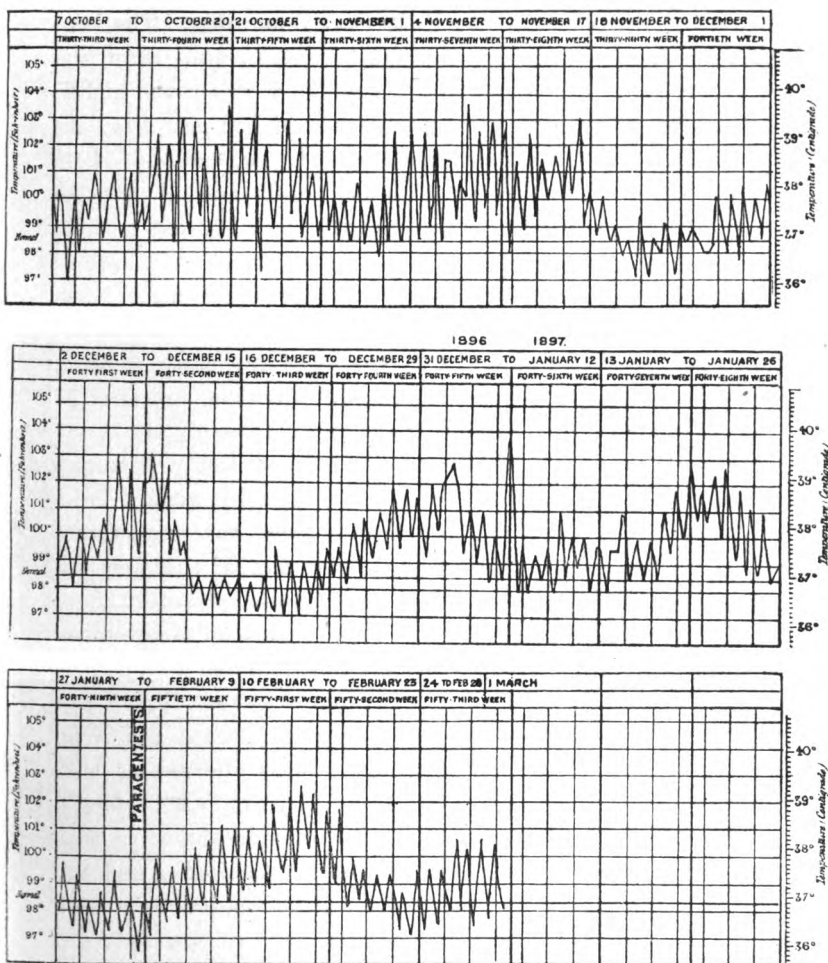
I saw him on February 1st and found clear serum in his right chest. He was then staying at Tunbridge Wells and he went home and was aspirated by Dr. F. R. B. Bisshopp, who drew off 18½ ounces. The fluid was examined by the Clinical Research Association, but no organisms were found in it. The media inoculated also remained perfectly sterile after forty-eight hours' incubation. The day after the aspiration the patient had a severe attack of chicken-pox with suppurating vesicles. After this came an exacerbation of fever which lasted from the 3rd to the 17th; the fluid appeared to be collecting again.

I saw him again at Tunbridge Wells on April 14th with Dr. Bisshopp. He was distinctly worse, anxious looking, thinner, paler, with patchy congestion of the face, rapid breathing, signs of fluid in the right chest but not more than there have been for some time, and not urgently demanding removal. The liver reached down to the umbilicus level, the spleen was much larger than it had been, coming within two inches of the umbilicus level, and nearly reaching the middle line. The urine contained a quantity of blood, and he complained bitterly of pain running down the left thigh. There was no swelling of the feet. The temperature for the four weeks previously had been oscillating between 99° and 103°.

On May 31st I heard that the pain in the left groin continued and extended to the foot, that there was no return of hæmaturia, but three or four attacks of hæmatemesis had occurred, and now there was some ascites. The feet were œdematous, and the urine contained one-sixteenth albumen. The temperature was 102° and 103°. A few fresh glands had appeared on the chest. On the 15th July he died.

24 *The Chronic Relapsing Pyrexia of Hodgkin's Disease.*





The following is an analysis of the temperature as shown in the above Charts :

For the first ten weeks, from February 26th to May 5th, the pyrexia was constant and of remitting type or intermitting type. The morning temperature was always below 98°4', often 98°, occasionally 97° or 97°5'. The evening temperature varied from 100° to 104°, so that the variations in the pyrexia were generally determined by the evening temperature. Sometimes, however,

the highest temperature was in the early morning. The least febrile temperature during that time was in the third and fourth weeks, in the fifth and sixth weeks it was much higher, in the seventh lower, in the eighth again higher, and from the middle of this week to the end of the tenth it gradually fell to normal. In the eleventh week it was nearly normal, only on five occasions above $98\cdot4^{\circ}$. The twelfth week showed a slight rise, never higher than $99\cdot5^{\circ}$. The next four weeks were covered by a curve of pyrexia with $100\cdot5^{\circ}$ as the maximum. Then followed two and a half weeks of a temperature never above 99° . Another curve (three and a half weeks) of moderate pyrexia, maximum, $100\cdot5^{\circ}$. One week of relative apyrexia, followed by two weeks' severe fever with evening temperatures of $101\cdot5^{\circ}$, and $103\cdot5^{\circ}$, and morning temperatures of 99° and 100° . A week's apyrexia brings us to the end of the twenty-sixth week. From this period to the end of the thirty-eighth week, the temperature was at a much higher range, almost like that of the first ten weeks, except that the morning temperature was more often above $98\cdot4^{\circ}$ than below it. Here again periods of fourteen to seventeen days with very high evening temperatures, alternated with periods seven to ten days with lower evening temperatures. From this period (the thirty-ninth week to the fifty-third week inclusive) there were five periods of pronounced fever alternating with shorter periods of less fever or actual apyrexia. The febrile periods differed now from those which preceded them, in that at the height of each the fever was more continuous, and the morning temperatures for five or seven days continuously were as high as $99\cdot5^{\circ}$ or 100° ; and in the apyrexial periods the morning temperatures fell lower than in preceding apyrexias, namely, to $97\cdot2^{\circ}$ and $97\cdot5^{\circ}$.

First period of ten weeks in which the temperature was above the normal, at least every evening:—

Exacerbation ...	14 days.			
Interval	14 days.
Exacerbation ...	14 "			
Interval	7 "
Exacerbation ...	21 "			

Second period of sixteen weeks in which the intervals were almost or wholly apyretic:—

Interval	7 days.
Pyrexia	...	35 days.		
Interval	18 "
Pyrexia	...	24 "		
Interval	7 "
Pyrexia	...	14 "		
Interval	7 "

Third period of twelve weeks in which the fever was again continuous, with exacerbations:—

Exacerbation	...	14 days.		
Interval	14 days.
Exacerbation	...	14 "		
Interval	7 "
Exacerbation	...	14 "		
Interval	7 "
Exacerbation	...	14 "		

Fourth period of fifteen weeks of pronounced fever, with intervals of much less fever or actual apyrexia:—

Interval	9 days.
Pyrexia	...	15 days.		
Interval	7 "
Pyrexia	...	19 "		
Imperfect interval		11 "
Pyrexia	...	10 "		
Interval	7 "
Pyrexia	...	19 "		
Interval	4 "
Pyrexia	...	4 or more.		

It may be very properly asked, What proportion do these cases of Hodgkin's disease with relapsing temperatures bear to the total number of cases? I have tried to answer this

question by a reference to the clinical records of Guy's Hospital, but the number of cases with complete records for a sufficiently long period is not large enough to give the information required. In the six years, 1898 to 1903 inclusive, I can find twenty-two cases recognised or diagnosed as Hodgkin's disease. One of these, my Case 2, I have already recorded. In seven of these cases the records of temperature are too imperfect to be of any value, or the charts have been mislaid.

In three cases the temperature was practically uniform over the short periods (seventeen days, seventeen days, and fifteen days) during which the patients were under observation. In one case death took place on the fourteenth day of residence, and the temperature, moderately febrile at first, was gradually and uniformly falling.

There remain six cases in which the relapsing tendency may be observed or suspected.

CASE 4.—A man, æt. 24, under Dr. Hale White. He was only in thirteen days, during which time the temperature was irregular. For two days it reached 102° in the evening, then for three days it was between 97° and 100° , then rose nearly to 103° and gradually fell to normal during five days. The time is, of course, too short to make it a very convincing case.

CASE 5.—A boy, æt. 17, in the Clinical ward, was under observation four weeks. During the first week the temperature rose to 101° , in the second week it was below 99° , but rose on the thirteenth day to 100° , and oscillated about this level during the third week. It was close down upon normal between the twenty-second and twenty-fifth days, and then rose again to 100° .

CASE 6.—A case under Dr. Hale White, in 1903, was under observation for eight and a half weeks, and showed relapsing periods, but they were not very pronounced.

CASE 7.—A boy, æt. $5\frac{1}{2}$ months, under Dr. Hale White, in 1902, had enlarged glands in the axilla, groin, and neck; a large

liver, large spleen and anæmia. He was admitted on September 26th and died on December 6th. From September 27th to October 1st there was pyrexia, gradually falling; and from October 2nd to October 5th the temperature was nearly normal. For the next eleven days there was a varying moderate fever; and from October 17th to November 4th a gradual rise to 102° . For the next three days the temperature was lower, and for the five days the record is missing. Then follow three days with a temperature no higher than 99.5° , and a temperature during seven days (November 16th to November 22nd) rising to 104° . During the remaining twelve days the temperature was again falling.

CASE 8.—A boy, æt. 17, was under my care in 1900, and his temperature was taken for the thirty days preceding his death. It was never below 98.4° , and rarely down to 99° ; for the first fifteen days it was chiefly between 101° and 104° ; during the next twelve days chiefly between 100° and 102° ; and it fell below 99° just before death.

This is in itself not a conclusive case, but if the temperature in the preceding months or weeks had been similar, there would have been a close resemblance to my case 8.

CASE 9.—This patient was in the Clinical ward in 1903 for twenty-five days, and the diagnosis from the general clinical conditions seems to have been rather uncertain. The cervical glands and the spleen were enlarged; there was anæmia of chlorotic type with leucopenia. From July 2nd to July 8th the temperature was 98° to 101.5° ; from July 9th to July 14th it fell to normal; it remained normal from July 14th to July 23rd, and then rose to nearly 100° .

A consideration of all the above cases, I think, leads us to the following conclusions:—

That a varying temperature is common in lymphadenoma.

That definite recurrences occur in some cases, the recurrences alternating with periods of complete apyrexia.

That the temperature may be continuously high for long periods, and that periods of higher fever may then alternate with periods of lower fever.

That the recognition of the relapsing form of pyrexia may be of great assistance in the diagnosis of some doubtful cases.

I do not like to dismiss the subject without referring to the opinion which has been strongly expressed, that Hodgkin's disease is a special form of tuberculosis. Musser,¹⁵ for instance, entertains this view; and he quotes Sternberg.¹⁶

Sternberg claims to have shown that in a large proportion of cases, described and regarded as Hodgkin's disease, and in some even of those in which relapsing pyrexia had occurred, lesions have been found in the lymphatic glands and other organs which are strongly suggestive of a tuberculous origin. There are necrotic and caseous foci of different sizes; and especially an abundance of peculiar large cells with one or more deeply staining nuclei of round, oval, or lobed.

Sometimes, but not in all cases, he was able to show the presence of tubercle bacilli; but in one case at least he was entirely unable to find any of these histological signs of tubercle. He appears to admit that this was an unequivocal case of Hodgkin's disease, and therefore that there may be, and is, a Hodgkin's disease apart from tubercle.

But even if it should subsequently prove that the tubercle bacillus or tubercle toxine has a share in the occurrence of Hodgkin's disease, it would still be of interest, if not of importance, to discriminate between the familiar cases in which tubercle leads to caseation and suppuration, with the possibility of recovery from its earlier stages, and those cases in which caseation and suppuration rarely occur, and which nevertheless

¹⁵ Loc. cit., p. 18.

¹⁶ Zeitschrift für Heilkunde, vol. xix., 1898, p. 21.

gradually progress to a fatal termination, chiefly by hæmorrhage and dropsy—a disturbance of the bodily functions which resembles those produced by the toxins or poisons of Bright's disease and of leukæmia, rather than by those of tubercle and its secondary pyogenic infections.

A short account of the first three cases here described, was contained in an address on "The Spleen and its Sufferings," delivered before the Midland Medical Society at Birmingham, November 9th, 1905, and published in the *Birmingham Medical Review*, November, 1905.

A short review of the subject is given by Dr. J. W. Russell in the *Birmingham Medical Review*, November, 1904, p. 672.

(Read before the Royal Medical and Chirurgical Society.)

MITRAL STENOSIS AND PREGNANCY.

By HERBERT FRENCH, M.D.,

AND

H. T. HICKS, F.R.C.S.

INTRODUCTION.

THERE is a large amount of literature upon this subject. Many of the papers contain accounts of small numbers of cases only. References are given at the end of this.

Berthiot's (3) book, published in 1876, and MacDonald's (11), published in 1878, have long been the standard works upon the subject. More recent publications which go fully into the question are those of Handfield-Jones (8) and Allyn (1), in 1896; Jess (9), who has collected all the published material upon the subject up to 1898; and Nicholson (13) and Mackenzie (12) in 1904.

There are certain points in regard to valvular heart disease and pregnancy upon which there is general agreement. These we do not propose to discuss further, because they appear to be well established. They are the following:

(1) Of all the varieties of chronic valvular heart disease, mitral stenosis is the most commonly accompanied by heart failure during pregnancy.

(2) Aortic lesions without mitral are rare in women ; few cases of pregnancy in women who have aortic without mitral disease come under observation.

(3) When symptoms of heart failure have preceded pregnancy they are made worse by pregnancy.

(4) Repeated pregnancies at short intervals cause greater risk of heart failure than do few pregnancies at longer intervals.

There are, on the other hand, some points upon which there is not the same agreement. Among these, one of the most important, perhaps, is the question of whether a young woman with mitral stenosis should marry. It is this question in particular that we devote our attention to in the present paper.

THE VIEWS OF OTHERS.

The serious view that has been taken of the prognosis in cases of mitral stenosis who become pregnant is shown by the following quotations :

Jellett, in his 'Manual of Midwifery,' 1905, p. 591, says: "Finally, the question must be answered, Should a woman with valvular disease marry? The answer to the friends or relatives of the patient must be 'No.' Our advice will probably not be taken, but, all the same, it should be given, and none the less definitely on that account. There is no use in 'hedging' by saying that if failure of compensation has ever occurred, or if the damage to the valve is considerable, or if some particular valve is affected, she should not marry. In view of the sequence of events which we know to be usual in any case of valvular lesion, and remembering that a woman has duties as a wife and as a mother which require her health and strength for their due performance, there should be no hesitation in the mind of the physician as to what answer he would give to such an inquiry. It is astonishing how frequently the question is raised in text-books and how evasively it is answered. That 'the perils of marriage should be clearly

stated to both the contracting parties,' as advised by a very recent American treatise on 'The Heart,' is not the way out of the difficulty. The physician has many puzzling questions to answer, but this is not one of them, and, as his opinion has been asked, it should be given in a definite and unequivocal manner."

P. Brouardel (21), quoting Pórak (22) ('Thèse d'Agrégation,' 1880, p. 109, "De l'influence réciproque de la grossesse et des maladies du cœur"), confirms the axiom, "Pour une cardiopathe, jeune fille, pas de mariage ; mariée, pas de grossesse."

These opinions are based upon the following statistics :—

MacDonald's figures :

	No. of cases.	No. of deaths.	Maternal mortality
Mitral stenosis	14	9	64·4 per cent.
Mitral regurgitation	8	3	37 „
Aortic regurgitation	5	2	40 „

Porak's figures :

	Premature births.	Maternal mortality.
Aortic lesions	25 per cent.	23 per cent.
Mitral regurgitation	50 „	13 „
Mitral stenosis	30 „	61 „
Mitral stenosis and regurgitation	42 „	45 „
Complex lesions	43 „	50 „

We would point out, however, that these statistics are based upon what are virtually selected cases. They only cover those in whom the cardiac symptoms had led the patients to seek medical advice. They do not include the cases in whom pregnancy produced little or no heart failure.

This is a very important omission. We have not been able to find an analysis of any large number of cases of women suffering from mitral stenosis in which this source of fallacy has been taken into account.

We have, therefore, analysed the obstetric histories of 300 consecutive cases of mitral stenosis in women over twenty, who have been in Guy's Hospital.

We realise that it is extremely difficult to be certain of the date at which a grown-up woman with valvular heart disease first acquired it. In many cases of mitral stenosis there is no history of acute rheumatism or chorea. The mitral stenosis may be proved by autopsy to be old. It is believed that such cases have had endocarditis in childhood, when the joint pains have been so slight that they have escaped the attention of the parents.¹

Even when there has been an attack of rheumatic fever in early youth there is often no means of determining with certainty that the valvular disease has dated from it. In our analysis we have excluded all cases where granular kidney was possible, and also those cases where the patient stated that rheumatic fever first occurred after twenty years of age. We have taken those in which the clinical diagnosis has been old-standing mitral stenosis, with or without other lesions, and in which there has been either rheumatic fever or chorea in childhood or youth, or no history of acute rheumatism at all. We have accepted the same evidence in all the cases, whether in married women not pregnant, in married women pregnant, or in single women over twenty, so that the analyses of each class are comparable. Our cases are given in tables at the end of the paper.

MANY MITRAL STENOSIS CASES BEAR CHILDREN WELL.

The likelihood is, that any woman who has mitral stenosis will, sooner or later, suffer from the results of failing compensation. There are all degrees of mitral

¹ Taylor, in 'The Practice of Medicine,' 1904, p. 157, says: "... the cardiac lesions may occur without any obvious affection of the joints at all. This greater liability on the part of the heart is especially frequent in children. . . ."

stenosis, and of the power of different hearts to maintain their compensation. Some hearts will fail early, whatever the woman does. Other hearts seem able to carry on their work almost as well as if no valvular disease were present. Even when heart failure comes on during pregnancy or the puerperium it is difficult to be sure that the heart would not have failed in any case, even had there been no pregnancy.

We have analysed our 300 cases as justly as we are able, attributing heart failure to child-bearing in as many as we felt we honestly could. We have come to the conclusion that the greater number of pregnancies in women with mitral stenosis, whose compensation has not previously failed, run their course as naturally as do the pregnancies of healthy people.

Thus, of the 300 consecutive cases, 205 were married. Of these, 135, or 66 per cent., did not attribute their ultimate heart failure to pregnancy, nor could we satisfy ourselves that there was any direct relation between the pregnancy and the heart failure. In one of these cases there had been as many as 17 children born alive, and the average number of children was 4.5 per mother. If 135 mothers with mitral stenosis can bear 608 children without losing cardiac compensation, it would seem unjust to prevent a young woman with compensated valvular heart-disease from getting married.

We found a direct relation between child-bearing and heart failure in 57 women, or 28 per cent. In many of these, however, there had been previous children born without trouble. In one case, indeed (No. 168), the labours with twelve children had been uneventful, heart failure occurring for the first time with the thirteenth. Upon twelve separate occasions this case might have come into our group of cases without heart symptoms; but the thirteenth transfers her to our group of cases where heart failure is related to pregnancy. It seems worth while to represent the relationship between pregnancy and heart failure in mitral stenosis in another way, as follows:

		Associated with heart failure.		Not associated with heart failure.
1st pregnancy	.	15	.	177
2nd	„	16	.	139
3rd	„	10	.	116
4th	„	14	.	95
5th	„	13	.	74
6th	„	14	.	61
7th	„	5	.	50
8th	„	8	.	38
9th	„	1	.	30
10th	„	2	.	26
11th	„	2	.	18
12th	„	2	.	13
13th	„	2	.	10
14th	„	0	.	7
15th	„	0	.	2
16th	„	0	.	2
17th	„	0	.	1

THE TIME AT WHICH, WHEN RELATED TO PREGNANCY, HEART
FAILURE SETS IN.

We appreciate fully the fact that an existing tendency to failure of compensation is aggravated by child-bearing. Some of these patients, when they do go wrong, break down badly. Others, however, respond no less readily to treatment than do non-pregnant cases. It is difficult to determine the prognosis in any given case.

Amongst the 57 patients (see Table, Nos. 149–192) in whom we relate the cardiac failure to child-bearing we were uncertain in 7 whether the symptoms came on before, during, or after the birth of the child. In the remaining 50, 25 dated their heart trouble to the time when they were carrying, 25 went to term without difficulty and the cardiac symptoms set in during the puerperium.

THE PROGNOSIS WHEN HEART FAILURE IS RELATED TO PREGNANCY, LABOUR, OR THE PUERPERIUM.

The prognosis in regard to heart cases is always difficult to estimate from hospital records. Many patients recover sufficiently to go away to their homes, but there is no evidence to show how long their cardiac compensation is maintained. Some such cases doubtless die comparatively soon. Others remain chronic invalids for years. A few recover sufficiently to do their work for a longer or shorter time. It is a matter of every-day experience to find heart cases, men and women alike, coming into hospital for a few weeks, recovering cardiac compensation to some extent, going away to their homes, only to return again and again to the hospital. Those who die at home are not heard of again. Those who recover completely for the time being are also lost sight of. They change their address and cannot be traced. There is the greatest difficulty, therefore, in determining whether women with mitral stenosis, whose cardiac compensation has broken down in relation to child-bearing, have a worse prospect of life than have other cases whose heart failure has been due to other causes.

The proportion who die in the hospital is really no criterion, because we do not know what proportion of the others die soon after discharge ; but since this source of error is common to all hospital statistics, we give the proportions for what they are worth :

(a) Of 135 mitral stenosis women who had borne children, but whose heart failure did not date from child-bearing, 44, or 33 per cent., died in hospital.

(b) Of 57 mitral stenosis women who had borne children, and whose heart failure did date from child-bearing, 20, or 35 per cent., died in hospital.

(c) Of 13 mitral stenosis women, married but never pregnant, 6, or 46 per cent., died in hospital.

(d) Of 95 mitral stenosis women, unmarried, 17, or 18 per cent., died in hospital.

At first sight this would seem to indicate that the prognosis was worst in the sterile women, best in the unmarried, intermediate in those who had had families. A glance at the relative ages in the different groups shows that this deduction is unwarranted; for the average age of all the cases in the four groups were :

	Average age. ¹	Maximum age.	Minimum age.
(a)	41 years	71	22
(b)	32 „	48	20
(c)	34 „	55	25
(d)	30 „	60	20

The average age of the single women was less than that of the married; the mortality amongst them should naturally be less. Could we trace the unmarried cases forward into the ten years to come, we should find that many would ultimately die in hospital, and some of these would probably have entered into the married state before they died. Many of our married cases had come in and out of hospital half a dozen times or more before they ultimately died.

We think the hospital mortality statistics afford no sound basis for any deduction; but if we drew any deduction at all it would be that, allowing for differences of age, the mortality of matrons is not materially different from that of spinsters, each having mitral stenosis.

THE PROGNOSIS WHEN HEART FAILURE SETS IN DURING PREGNANCY.

The paragraph above indicates how difficult it is to say whether or not a given woman, a hospital patient suffering from mitral stenosis, with symptoms of heart failure, will ultimately die in hospital or not. It is less difficult to

¹ The average age at death of married women with mitral stenosis is obviously less than that of healthy women. If the fact that the wife is likely to predecease the husband is regarded as a bar to marriage in all cases, then we agree that women with mitral stenosis should not marry. Our point is that we think the grave influence of pregnancy upon mitral stenosis has been over-estimated.

say whether or not a given woman, being pregnant, and admitted to hospital with cardiac symptoms from mitral stenosis, will leave the hospital alive, and whether or not she will approximately reach term and bear a living child.

Amongst our 300 consecutive cases, 22 were admitted whilst actually pregnant. For the details of these we refer to the table at the end of the paper, Cases Nos. 4, 5, 8, 149, 151, 152, 153, 155, 161, 163, 165, 166, 168, 169, 171, 174, 177, 178, 180, 182, 183, 184. In addition to these, we have found fourteen other pregnant mitral stenosis patients, who came into the hospital either before or after the period of our 300 consecutive cases. The following are notes of these additional patients :

(i) Aged 43. She was admitted for retroverted gravid uterus, and had no cardiac symptoms ; there was well-marked mitral stenosis. The uterus was replaced, the patient being in the ward only five days. She had been married fifteen years, had had seven living children and one miscarriage. The last labour was seventeen months before, at full term. She was now pregnant four months.

(ii) Aged 36. She was admitted when seven months pregnant for orthopnoea, precordial pain, hæmoptysis, and bronchitis, without oedema. She gave no history of acute rheumatism, but was found to have old mitral stenosis. With rest in bed and digitalis she improved rapidly. She went to term. The labour was natural. The mother and child both did well. She had had ten living previously, and with each pregnancy had had some dyspnoea in the later months, but recovered completely soon after labour.

(iii) Aged 22. She was admitted when eight months pregnant for her eleventh attack of acute rheumatism. She had mitral stenosis and regurgitation, and aortic stenosis and regurgitation, but neither now nor previously had she suffered from her heart. She went to term ; labour was natural ; mother and child did well. She had

had one child previously, stillborn at full term, without difficulty. She had been in Guy's Hospital eleven times before, once for hæmatemesis and (?) gastric ulcer, ten times for acute rheumatism. The heart lesion was old.

(iv) Aged 40. She had been married only six months, and was five months pregnant on admission. She came in for dyspnœa. She rested in bed for a fortnight, and went out on the twenty-fourth day, free from dyspnœa, still pregnant. The heart lesion was old mitral stenosis.

(v) Aged 25. She came in for dyspnœa when four months pregnant, and was found to have a large irregular heart and mitral stenosis and regurgitation. She was only in the ward six days, when she went home of her own accord, still pregnant. She had had rheumatic fever four times.

(vi) Aged 19. She came in when pregnant nearly to term for a sudden hemiplegia. This was found to be due to cerebral embolism from mitral stenosis. There were no cardiac symptoms. She went to term. Labour was natural. Mother and child did well, but the hemiplegia recovered but partially. There was weakness of the affected side a year later, but no heart failure. There was no history of rheumatic fever.

(vii) Aged 33. She came in for acute bronchitis and orthopnœa, without œdema, when six months pregnant. She was found to have mitral stenosis, but gave no history of acute rheumatism. She was immediately relieved by rest in bed, and went out in fifteen days, still pregnant. She had had some trouble with her first pregnancy, but had recovered completely, and had borne seven living children.

(viii) Aged 20. She had had acute rheumatism many times, first when eleven. She had aortic stenosis and regurgitation, and mitral stenosis and regurgitation. She had had one living child two years before without difficulty,

and had now missed two menstrual periods. Up till just before admission she had worked hard at a jam factory, carrying trays of jars of jam up and down stairs. She was seized with acute rheumatism again, and came to hospital with a certain amount of dyspnœa also. She rested in bed, recovered rapidly, and went out on the twentieth day, able to walk actively without dyspnœa. It was jam-jar carrying rather than pregnancy that had caused the cardiac symptoms.

(ix) Aged 29. She gave no history of acute rheumatism, but had old mitral stenosis. She had had four children previously without difficulty. Eighteen days before admission orthopnœa and cough came on simultaneously with an abortion. She was attended by the Charity and transferred to the wards. She rested, and had digitalis; on the twenty-sixth day she went out, free from dyspnœa.

(x) Aged 25. She had had acute rheumatism at sixteen and at twenty-one. She came in for dyspnœa in the later months of pregnancy, and was found to have mitral disease. The notes are incomplete; it is not known if she was married nor if she had had a previous pregnancy. With rest and digitalis she became free from dyspnœa, and went out on the twenty-fourth day, still pregnant.

(xi) Aged 27. She had had no acute rheumatism, but had old mitral stenosis. She had been married four years. Her first pregnancy ended at the seventh month in delivery of a still-born child. The second pregnancy went to term naturally, and there was no heart failure, but when two and a half months pregnant she had a "fit," which left her with hemiplegia. This passed off completely after labour. Dyspnœa first began fourteen months ago, and on admission she was eight and a half months pregnant, orthopnœic, and cyanosed. With rest in bed and digitalis she reached full term, and was delivered of a living female child weighing 6 lb. 8 oz. Both mother and child did well, and went out early in the puerperium. The

dyspnœa was still present on exertion, but not with ordinary walking.

This patient foolishly became pregnant again a year and a half later. She was admitted at the fourth month for hæmatemesis, and rapidly recovered from this, but all through the pregnancy there was severe dyspnœa and swelling of the feet. Cyanosis became extreme, and just before term labour was induced. Delivery was spontaneous twenty-four hours later, and was accompanied by post-partum hæmorrhage. The child was 17 inches long, weighed 6 lb. 8 oz., and lived. The mother had severe dyspnœa and bronchitis during the early part of the puerperium, but under treatment the œdema disappeared and the cough decreased. She walked from the hospital, but readily became dyspnœic on exertion.

(xii) Aged 22. She gave no history of acute rheumatism, but was found to have mitral stenosis. She did not come in for heart failure in the ordinary sense, but for acute pericarditis. She refused to stay in the hospital. On the third day she insisted on going home, notwithstanding that she had acute pericarditis and was very seriously ill. She was pregnant five months at this time, and had borne one child eighteen months previously without developing cardiac symptoms.

(xiii) Aged 26. She gave no history of acute rheumatism, but died, and was found to have chronic valvular heart disease, both aortic and mitral, and a fatty heart. She had been married a year, and was pregnant nearly to term. She had developed acute dyspnœa three weeks before. Labour was induced and a living male child born. The patient became much worse the day after the confinement, and the heart did not respond to any treatment. The mother died on the ninth day after labour, the child lived.

(xiv) Aged 24. She gave no history of acute rheumatism, but had mitral stenosis. She had had twins prematurely

thirteen months before. The infants were born living, but both died. There had been no cardiac symptoms with that pregnancy. When five months pregnant for the second time she became very dyspnoëic and cyanosed. When admitted, it was thought she must die; she recovered rapidly with rest in bed and digitalis, and was able to go home, still pregnant. She was re-admitted at the seventh month, extremely dyspnoëic, with œdematous legs and a rapid, irregular pulse. She was venesected and given digitalis, and rested in bed. The pregnancy continued naturally; the cardiac symptoms all abated; she was delivered at full term of a living child weighing 5 lb. 6 oz. Both mother and child did well, and the mother was free from dyspnoea on ordinary exertion when she left the hospital.

We have, therefore, 36 cases in which mitral stenosis patients have come into Guy's Hospital when pregnant. These are all we have been able to find in a period of over twenty-five years. Leaving out cases under twenty years of age, the number of women with mitral stenosis who were admitted during the same period was something like 750. If cardiac symptoms from mitral stenosis were the rule during pregnancy, surely more cases would have sought admission when actually pregnant.

Of the 36 patients, not one died during pregnancy, if we exclude Cases No. 149 and xii, who refused to stay in, and whose fate is not known. Not one died during labour. Nine had no heart failure, but came in for other things (Nos. 4, 5, 8, 165, 168, i, iii, vi, xii). Twenty-four went out with restored cardiac compensation (Nos. 4, 5, 8, 151, 152, 153, 155, 161, 163, 165, 166, 168, 169, 171, i, ii, iii, iv, vi, vii, viii, ix, x, xiv). Only five died within three months of labour (Nos. 174, 177, 180, 183, xiii), and of these one (No. 180) died, not of mitral stenosis, but of chorea gravis and infective endocarditis.

In regard to the children, the fate of ten is unknown, because the mothers recovered and went out to be delivered elsewhere. Of the remaining 27, 23, including

twins in one case, were born living, at term, or within a month of term (Nos. 4, 5, 8, 151, 155, 161, 163, 165, 166 (twins), 169, 174, 177, 178, 182, 183, ii, iii, vi, xi (?), xiii, xiv). In two cases (Nos. 153, 171) the child was born at or near term, but dead. There were two abortions (Nos. 180, ix), and the former of these two was due to chorea gravis.

These figures are very different from those of MacDonald (11), as will be seen by comparing them side by side :

	No. of cases.	Maternal mortality within three months.	Abortions.	Lesion.
MACDONALD : (Published cases)	14	64·4 per cent.	14·3 per cent.	Chronic mitral stenosis only.
OURSELVES : (Consecutive hospital cases)	36	13·9 „	5·5 „	Chronic mitral stenosis, with or without other lesions.

We very much wish we had a larger number of cases in which the course of pregnancy in mitral stenosis had actually been observed in hospital. We feel that the great difference between MacDonald's statistics and our own is in part due to the small number of cases we each have. Nevertheless we feel convinced that MacDonald's figures overstate the seriousness of the prognosis. His own words are : "We have thus nine cases out of fourteen, or 64·4 per cent., fatal, which indicates a tendency to death which is surely sufficiently grave. It will be observed that the deaths occurred either suddenly during the labour or within a few days or weeks afterwards." We agree that the cardiac failure, once begun, may become very grave during the puerperium, but we have no single instance in which death occurred during labour.

The patients behave very much like other cases of heart disease. Even when the heart condition seems hopeless they may recover and bear other children. An instance in point is No. 169, whose history was shortly as follows :

She became dyspnoëic during her first pregnancy, and

had had cardiac trouble many times since. On two separate occasions her symptoms were so grave that labour was induced at the eighth month ; on one of these there was post-partum hæmorrhage, which nearly proved fatal. After her fourth child she was discharged from the hospital, with the note in her report that she was "a wreck" ; at that time it was thought impossible that she could live, but she recovered at home, and bore two more children. The last, and sixth, was born at term, without induction of labour ; it was a transverse presentation, and version had to be performed ; the mother and child both did well.

THE TREATMENT OF MITRAL STENOSIS CASES WHEN PREGNANT.

The cases of mitral stenosis who have come into Guy's Hospital pregnant have, almost without exception, been treated as though they had not been pregnant. Rest in bed, with digitalis, given with the same precautions as in other cases, have almost invariably brought relief, and enabled the patient to go on to natural labour at or near term. Induction of labour has hardly ever been resorted to, as reference to the cases at the end of this paper shows. Labours have in almost all cases been easy and natural, and free from post-partum hæmorrhage.

It is true that the same might not hold good for ladies in higher ranks of life. The physical work of Borough women is hard, that of most well-to-do women is less so. The relief to the Borough woman's heart is proportionately greater than is that to the rich lady's when she goes to bed. Nevertheless, we hold the view that the treatment of a pregnant woman with mitral stenosis should not be different from that of a non-pregnant woman with the same heart lesion. If the patient can be up and about, without cardiac symptoms, it is better for her to live as usual, and by moderate exercise maintain the reserve power of her heart, rather than lie up and diminish this

reserve power by prolonged rest. If cardiac symptoms supervene, the treatment should then be rest on a couch for mild cases, rest in bed for severer cases, rest in bed and digitalis for severer still. The pregnancy should, if possible, be allowed to run its course. Induction of labour in cardiac cases brings no immediate abatement of symptoms, as it does in many cases of eclampsia, for example. The puerperium is not less dangerous than is pregnancy itself to a case of mitral stenosis. The cardiac condition should be restored to as fair a state of compensation as possible before the time of labour arrives, and then forceps may be used to assist Nature. In a word, treat the patients exactly as though they were non-pregnant; treat them for mitral stenosis, do not treat them for pregnancy.

STERILITY IN MITRAL STENOSIS.

The opinion has been expressed that many women with mitral stenosis are sterile. Allyn (1), for example, says that "mitral disease, particularly stenosis, is much graver, as a rule, than aortic, but there is an attempt at a natural prevention of this, owing to the high proportion of sterile women among the subjects of mitral stenosis."

We do not agree with this. Out of the 205 married women in our table, only thirteen had not been pregnant. One of these had but recently got married, so that the proportion of presumably sterile women was only 5·8 per cent. The remainder had borne, upon the average, between four and five children apiece.

THE LIABILITY TO ABORTION IN MITRAL STENOSIS.

Allyn (1), quoting Porak (22), states that cardiac disease in the mother has a very grave influence upon the foetus, abortion being very common.

Unfortunately, this point was not particularly attended to in many of our cases. In our epitomes we have only put down whether abortions had occurred or not when we

had definite statements from the patient to that effect. We have left the doubtful cases blank.

In 90 of the women who had been pregnant we ascertained the history in regard to abortions, and found 40 of them had never had any abortion at all. The remainder had had 91 abortions between them. The general average was thus 1 per mother. The majority did not tend to abort, but in a few there were repeated abortions—in Case No. 56 as many as six.

It will be noticed that some of the abortions occurred when there was no heart failure at all. In these the association was possibly adventitious. In others the heart failure dated from an abortion, and it seems likely that in some of these the heart trouble was directly responsible for the miscarriage.

Upon the whole, however, we do not think that the tendency to abortion is obviously greater amongst mitral stenosis cases than it is amongst other Borough women.

CASES IN WHOM WE KNOW THE MITRAL STENOSIS CERTAINLY ANTEDATED THE PREGNANCIES.

As we have pointed out in the early part of this paper, it is impossible to state with absolute certainty that the mitral stenosis was present before marriage in a large number of cases. We have said that this is a flaw in our arguments, and might render the deductions we have drawn from our 300 cases invalid. There are, however, a small number who had been in the hospital, or under observation, years previously, and in whom we know that mitral stenosis was present before marriage. We will now consider these, seventeen in number, by themselves, and see whether what we have said about the generality of the cases holds good of these also.

CASE No. 6.—Valvular disease was known to exist at ten. There had been one child, and there had never been cardiac symptoms. The patient was admitted for a

fourth attack of acute rheumatism, with good cardiac compensation.

CASE No. 12.—There had been acute pericarditis before marriage. There had been one living child and one miscarriage. The patient was admitted for recent cardiac symptoms, not related to child-bearing.

CASE No. 59.—The physical signs of mitral disease had been present for thirty years. The patient had borne ten children without difficulty. Heart failure did not set in till she was fifty-six.

CASE No. 75.—The mitral bruits were present at twelve. The patient had had five children. She came in for acute rheumatism, and had never had cardiac failure.

CASE No. 89.—Heart disease was known at fourteen. There had been one child, without difficulty. The patient came in for lobar pneumonia, and recovered without a symptom of heart failure.

CASE No. 90.—The bruits were known before marriage. There had been three children, born without difficulty.

CASE No. 91.—The bruits were known before marriage. The patient bore five children, and her heart failure did not come on in relation to any of these.

CASE No. 92.—Heart disease was known at thirteen. There had been three children, pregnancies and labours being uneventful.

CASE No. 93.—Heart disease was known at thirteen. There had been four children and two miscarriages, without trouble.

CASE No. 94.—Heart disease was known at sixteen. The four children had been born without cardiac symptoms.

CASE No. 95.—Heart disease had been known for ten years. There had been eight children, and no heart failure with any of them.

CASE No. 96.—Heart disease was known in girlhood. There had been one child, born without trouble.

CASE No. 97.—The bruits were known to be present at nineteen. There had been one child, born without trouble.

CASE No. 138.—Heart disease was known at sixteen. There had been six children. Cough and dyspnoea had occurred during each pregnancy, but there had been good recovery of compensation each time.

CASE No. 148.—Heart disease was known at sixteen. The first five children had caused no cardiac symptoms. Failure of compensation set in with the sixth.

CASE No. 153.—This patient had been in and out of hospital seven times for heart failure before marriage. She married notwithstanding. The cardiac symptoms were severe during pregnancy. A dead child was born at the eighth month. The mother recovered rapidly enough to leave the hospital on the fourteenth day after labour.

CASE No. 161.—This patient was in hospital when eighteen for heart disease. She married after this, and bore four children without heart trouble. When pregnant with her fifth child, cardiac symptoms appeared. The patient lay up in hospital for four days only, and then went home and went naturally to term.

There were, it will be seen, many children borne by women who were known to have heart disease before marriage. In 13, or 76·5 per cent., the ultimate heart failure was not directly related to child-bearing. In 4, or 23·5 per cent., pregnancy and heart failure coincided, but even in some of these previous children had been born without causing heart trouble. None of the patients died during pregnancy or labour. All recovered and left the hospital.

If we compare these figures with those for the generality of women with mitral stenosis; we find—

	Heart failure not directly related to pregnancy.	Heart failure directly related to a pregnancy not necessarily the first.
When the mitral stenosis was old, but of unknown date (175 cases, taken con- secutively)	69.7 per cent.	30.3 per cent.
When the mitral stenosis was known with certainty to date from before marriage (17 cases, taken consecu- tively)	76.5 „	23.5 „

The results are closely similar. We are fully conscious that the number of cases in which we know the mitral stenosis certainly preceded marriage is small. In the remainder the evidence that the mitral stenosis was present before marriage is presumptive only. We do not know how to collect a large number of cases where this presumption is avoidable. We have taken only those cases where the bruits suggested an old-standing valvular lesion, and have only accepted cases where there had either been acute rheumatism or chorea in youth or else no rheumatism at all. The fact that the results are so similar in the total number of cases to what they are in those where heart disease was known to antedate the pregnancies affords, we think, additional ground for the justness of the conclusions we have drawn.

ASSOCIATION OF OTHER HEART LESIONS WITH THE MITRAL STENOSIS.

Most observers are of the opinion that the prognosis is less good when aortic or other disease is present as well as mitral stenosis. We have taken our cases consecutively as they entered the hospital, and have made no distinction between cases where mitral stenosis alone was diagnosed and those where other lesions of the heart were present also. Amongst the associated lesions will be found mitral regurgitation, aortic regurgitation, aortic stenosis, aortic stenosis and regurgitation, pulmonary stenosis, tricuspid stenosis, pericarditis, and adherent pericardium. Notes

of these are given in the epitome of cases in the table at the end of this paper. They should make the prognosis in the affected cases proportionately worse. We do not intend to enter upon this question here. We have discussed the cases as though they were suffering from mitral stenosis only.

THE INCIDENCE OF FUNGATING ENDOCARDITIS.

In all the patients who died the diagnosis was verified by autopsy. We have been struck by the large proportion of mitral stenosis cases who die of a terminal fungating endocarditis. Thus—

Of 43 fatal cases where failure was not dated to pregnancy, 10, or 23 per cent., died of fungating endocarditis.

Of 22 fatal cases where failure was dated to pregnancy, 9, or 41 per cent., died of fungating endocarditis.

Of 6 fatal cases who were married, but had not been pregnant, 0 per cent. died of fungating endocarditis.

Of 18 fatal cases who were single, 7, or 39 per cent., died of fungating endocarditis.

Of the total 89 fatal cases, 26, or 29 per cent., died of fungating endocarditis.

At first we thought there might be a special tendency for pregnancy or the puerperium to lead to fungating endocarditis, but we do not think this can really be so, seeing how high the proportion of cases of terminal fungating endocarditis is in single women with old mitral stenosis.

SUMMARY.

We believe that heart failure is to be expected sooner or later in almost all cases of valvular heart disease.

We do not deny that pregnancy may cause serious, and even fatal, cardiac failure in cases of mitral stenosis.

We think, however, that the dangers of pregnancy in these cases have been overstated.

We attribute the overstatement to the fact that previous

statistics have been based mainly upon cases of mitral stenosis which came under observation because heart failure had developed during, or soon after, pregnancy. We feel that statistics so obtained leave out of count all those cases of mitral stenosis who go through pregnancy without developing cardiac symptoms.

We have tried to obviate this source of error by analysing the obstetric histories of 300 women over twenty who had mitral stenosis with or without other lesions. We have not selected our cases, but have taken them consecutively as they came into Guy's Hospital.

We conclude :

- (1) That comparatively few are sterile.
- (2) That they are not especially liable to abort.
- (3) That the majority bear children well.
- (4) That when heart failure develops in relation to pregnancy it is very often not with the first pregnancy, but after several.
- (5) That the treatment should be the same as for a non-pregnant case of mitral stenosis.
- (6) That it is not just to absolutely negative marriage in all women with mitral stenosis. The dogmatic "no" of Jellett and of Porak (p. 34) is, we think, unjustifiable. It is right that the physician should make clear to the contracting couple, or to their near relatives, the risk run. He should use his discretion, and distinguish between one case and another. The risk should not be minimised, but it should not be exaggerated. Whether the woman marry or not, it is likely that she will not reach old age. She should not have successive children rapidly. But if she has survived the age of twenty, with good cardiac compensation, the likelihood that pregnancy will accelerate the time of heart failure does not seem to be so great as has in text-books been declared.

We thank the Treasurer of Guy's Hospital and the Physicians to Guy's Hospital for their kind permission to use the statistics embodied in this paper.

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ANALYSIS OF 300 CONSECUTIVE CASES OF MITRAL STENOSIS, WITH SPECIAL REFERENCE TO PREGNANCY AND LABOUR. NO CASE IS INCLUDED UNDER THE AGE OF 20; AND IN ALL RHEUMATISM OR CHOREA HAD OCCURRED BEFORE 20, OR NOT AT ALL.

A. Those who had been Pregnant, and did not die Cardiac Symptoms to Pregnancy or Labour.

Case number.	Age.	Age at which rheumatism or chorea.	Number of children.	Number of miscarriages.	Main diagnosis.	Symptoms for which admitted.	Duration of cardiac failure.	Details.	Re-sult.*
1	22	None	1	0	Mitral stenosis, acute bronchitis, erythema nodosum	Oedema and dyspnoea	7 weeks	Married 18 months. One child, full term, 8½ months ago without trouble	R.
2	24	19	1	0	Mitral stenosis and regurgitation, infective endocarditis, various emboli	Pyrexia and rigors	No heart failure	The pyrexia and sepsis date from 1 month after labour; the pregnancy and labour had been free from cardiac symptoms. The infection may have been directly due to the puerperium, but there was no cardiac failure	D.
3	25	None	1	0	Lobar pneumonia (double), mitral stenosis	Pneumonic	No heart failure	The child was born at full term 12 days before admission. There were no cardiac symptoms at all	R.
4	27	"	3	0	Chorea, mitral stenosis	Chorea	Ditto	Two full-term children without trouble. At present 7 months pregnant; subsequently went to term without cardiac symptoms	R.
5	27	13	1	0	"	"	Ditto	Patient unmarried, and 4½ months pregnant on admission. Recovered from chorea; went to term naturally	R.
6	27	6	1	0	Acute rheumatism (4th), mitral stenosis	Rheumatism	Ditto	Known to have had heart disease at 10; no cardiac symptoms since	R.
7	33	10	4+ 1 D†	1	Acute rheumatism (2nd), mitral stenosis and regurgitation	"	Ditto	Last confinement was 4 years ago; miscarriage 10 weeks ago. No heart failure at labours	R.

* R. = recovered and went home. D. = died in hospital.

† D. = stillborn.

Case number.	Age.	Age at which rheumatism or chorea.	Number of children.	Number of miscarriages.	Main diagnosis.	Symptoms for which admitted.	Duration of cardiac failure.	Details.	Result.
8	36	None	8	0	Acute rheumatism (1st), old mitral stenosis	Rheumatism	No heart failure	Had had 7 children, last 2 years ago. Now admitted at term; labour natural; no cardiac failure	R.
9	25	18	3	0	Cerebral embolism, mitral stenosis and regurgitation	Hemiplegia	Ditto	First child born at 18, second at 19, third at 28; no cardiac failure with any of them. Transient hemiplegia 14 months ago; complete, 7 months ago. The child was born without trouble 2 years ago	R.
10	24	15	1	—*	Mitral stenosis and regurgitation, bronchitis, enlarged liver	Precordial pain and dyspnoea	1 month		R.
11	28	None	3	2	Mitral stenosis, tricuspid regurgitation, oedema	Cyanosis and dyspnoea	3 weeks	There had been no cardiac symptoms with any of the pregnancies	R.
12	30	20	1	1	Mitral stenosis and regurgitation	Dyspnoea	Acute	There had been pericarditis before marriage; the pregnancies had been uneventful	R.
13	31	16	2	—	Mitral stenosis and regurgitation, pleurisy with effusion	"	1 year	Pregnancies uneventful	R.
14	32	14	2	—	Mitral stenosis and regurgitation	"	Recent	"	R.
15	32	None	1	—	Mitral stenosis, tricuspid regurgitation	Ascites	3 months	Child was born 7 years before	R.
16	33	Childhood	5	—	Mitral stenosis and regurgitation, tricuspid regurgitation, pleurisy	Dyspnoea and rheumatism	Recent	Last child was born 2 years before, without trouble	R.
17	34	None	1	0	Mitral stenosis and regurgitation, tricuspid regurgitation	Oedema	"	Child was born 5 years before	R.

* The mark — signifies that it is not known whether there has been any miscarriages or not.

18	36	None	1	—	Mitral stenosis and regurgitation	Œdema and dyspnoea	5 years off and on; acute 8 weeks	Child was born 11 years ago, without cardiac trouble	R.
19	36	"	2	—	Mitral stenosis, aortic regurgitation	Precordial pain, anginal	Acute 14 days	Pain of an anginal character had been present off and on for several years; the pregnancies had been uneventful, without heart failure or increase of pain	R.
20	36	19	6	—	Mitral stenosis, aortic stenosis and regurgitation	Dyspnoea and œdema	18 months off and on; acute 3 months	There had been no dyspnoea except on exertion until quite lately; the pregnancies had occurred without heart failure	R.
21	36	Childhood.	6	—	Mitral stenosis and regurgitation	Dyspnoea and cough	Acute recently	She had not noticed any cardiac symptoms until 3 years before; the pregnancies had been uneventful	R.
22	37	16	2 + 1½*	2	Mitral stenosis and regurgitation	Dyspnoea	Recent	The patient stated that she had not felt thoroughly well for many years; had had no trouble with any pregnancy or labour, and had only recently felt worse than usual	R.
23	38	8	3 + 1 d.	—	Mitral stenosis and regurgitation, tricuspid regurgitation	Œdema and dyspnoea	1 year	Pregnancies uneventful	D.
24	38	Childhood	8	2	Mitral stenosis	Dyspnoea and precordial pain	On and off for 12 years; acute 1 month	Had been married 18 years. Though there had been shortness of breath on exertion for 12 years, the pregnancies had not caused any serious trouble	R.
25	38	16	2	0	"	Œdema of legs	14 days	Last child was born 14 years ago	R.
26	38	None	8	—	Mitral stenosis, tricuspid regurgitation, big liver	Hæmoptysis and hepatic pain	2 weeks	There had been twins twice. With each of these there had been hæmoptysis, but beyond that no heart trouble till 2 weeks ago	R.
27	39	None	6	—	Mitral stenosis and regurgitation, big liver, ascites	Œdema and ascites	2 months	Pregnancies uneventful	R.
28	39	Childhood	2	1	Mitral stenosis and regurgitation, tricuspid regurgitation, ascites	Dropsy	2 months	"	R.

* 1½ = 7 months child.

Case number.	Age.	Age at which rheumatism or chorea.	Number of children.	Number of miscarriages.	Main diagnosis.	Symptoms for which admitted.	Duration of cardiac failure.	Details.	Result.
29	39	None	8	4	Mitral stenosis and regurgitation, pericarditis	Precordial pain	Acute	Pericarditis was the main cause for admission. No previous heart failure	R.
30	39	"	3	—	Mitral stenosis	Dyspnoea	On and off for 4 years	Last child 12 years ago	R.
31	40	"	13	—	Mitral stenosis, big liver	Dyspnoea and oedema	On and off for 7 years; acute for 5 months	Pregnancies uneventful	R.
32	40	14	1	0	Mitral stenosis, aortic regurgitation, tricuspid regurgitation	Palpitations and oedema	12 years on and off	Child 23 years ago	R.
33	40	None	0	2	Mitral stenosis and bronchitis	Dyspnoea	2 years on and off	Miscarriages were 20 years ago with first husband. Married a second time, no children	R.
34	42	"	2	—	Mitral stenosis, tricuspid regurgitation, bronchitis	"	Ditto	There was hemiplegia 11 years ago; the pregnancies were uneventful, and there was no cardiac failure till 2 years ago	R.
35	42	Girlhood	4	—	Mitral stenosis and regurgitation, ascites	Edema and ascites	2½ years on and off	Last child 6 years ago	R.
36	43	None	1 + 3 d.	1	Mitral stenosis and regurgitation	Dyspnoea and precordial pain	2 years	Last child 7 years ago	R.
37	43	20	8	—	Mitral stenosis, tricuspid regurgitation	Dyspnoea and cough	8 years off and on	Last pregnancy long preceded heart symptoms	R.
38	43	3	3	3	Mitral stenosis and regurgitation	Ditto	14 days	Pregnancies uneventful; miscarriages without heart failure	R.
39	43	17	1	—	Mitral stenosis and regurgitation, aortic stenosis and regurgitation	Edema and cough, ascites	2 years, ascites 6 weeks	The pregnancy was 25 years ago	R.

40	44	10	2	0	Mitral stenosis	Dyspnoea and precordial pain	Slight	The patient was married at 17 and quickly had 2 children	R.
41	44	9	1+	1	Mitral stenosis, angina pectoris	Angina	6 years	Pregnancies uneventful	R.
42	45	None	1 d.	—	Aortic stenosis and regurgitation, mitral regurgitation, pericarditis	hæmoptysis Precordial pain and dyspnoea	2 months	Child was stillborn 20 years ago	R.
43	46	14	7	0	Mitral stenosis and regurgitation, aortic stenosis, pleurisy	Acute pleuritic pain	None	Last child 6 years ago	R.
44	47	20	8	—	Mitral stenosis and regurgitation	Bronchitis and oedema	5 months	Pregnancies uneventful. Quite well till hæmoptysis 5 months ago	R.
45	47	18	4	0	Mitral stenosis and regurgitation, bronchitis	Cough	3 years on and off	Married at 18; youngest child is 25	R.
46	47	None	14	1	Mitral stenosis and regurgitation, big liver	Dyspnoea and vomiting	4 days	Last pregnancy 2 years ago	R.
47	47	11	2	—	Mitral stenosis and regurgitation, bronchitis, big liver	Œdema and cough	6 weeks	Last child 20 years ago	R.
48	47	None	6	1	Mitral stenosis	Œdema and palpitations	2 months	Married at 15; pregnancies uneventful	R.
49	48	16	9	—	Mitral stenosis and regurgitation; hæmaturia	Dyspnoea	6 months	Married at 19; pregnancies uneventful	R.
50	49	None	14+	1	Mitral stenosis and regurgitation, ascites	Œdema	2 years	Married twice. 8 and miscarriage by first husband; 6 and 1 still-born at 7 months by second	R.
51	50	"	11	—	Mitral stenosis and regurgitation	Palpitations and oedema	3 years on and off	Last child 7 years ago; patient has been a widow for 5 years	R.
52	50	"	9	—	Mitral stenosis	Dyspnoea and oedema	6 years off and on	Pregnancies uneventful	R.
53	51	"	14	—	Mitral stenosis and regurgitation, aortic stenosis and regurgitation	Anasarca	3 years	" "	R.
54	53	14	1	—	Mitral stenosis and regurgitation	Dyspnoea	2½ years	Child born many years before	R.

Case number.	Age.	Age at which rheumatism or chorea.	Number of children.	Number of miscarriages.	Main diagnosis.	Symptoms for which admitted.	Duration of cardiac failure.	Details.	Result.
55	53	None	17	—	Mitral stenosis and regurgitation, tri-cuspid regurgitation, ascites	Dyspnoea and œdema	1 year	Pregnancies uneventful	R.
56	54	7	2	6	Mitral stenosis, bronchitis, extreme cyanosis	Dyspnoea	1 month	"	R.
57	55	15	14	—	Mitral stenosis and regurgitation, bronchitis	Dyspnoea and œdema	1 year	Last child 15 years ago	D.
58	56	20	14	—	Mitral stenosis, ascites	Cough and œdema	10 weeks	Married at 20, and had her children quickly and without heart trouble	R.
59	56	15	10	—	Mitral stenosis	Dyspnoea and œdema	1 year	There was no trouble with pregnancies, except that the first and last labours were prolonged. The physical signs of heart disease were known 30 years before; failure was recent	R.
60	58	16	6	—	Mitral stenosis and regurgitation	Ditto	3 years	Pregnancies uneventful	R.
61	59	None	3	—	Mitral stenosis, aortic regurgitation, ascites	Dyspnoea	9 months	Sent to an infirmary a wreck; in all probability died soon after	D.
62	64	16	1	—	Mitral stenosis and regurgitation	Dyspnoea and cough	1 year	Child born soon after marriage at 23	R.
63	69	None	9	2	Mitral stenosis, pleurisy	Cough and chest pain	3 years	Pregnancies uneventful	R.
64	71	"	4	—	Mitral stenosis	Palpitations	6 months	"	R.
65	22	10	1	0	Mitral stenosis and regurgitation, acute rheumatism	Rheumatism	None	Child born a year before, without heart symptoms	R.

66	22	15	1	0	Mitral stenosis and regurgitation, acute rheumatism	Rheumatism	None	Child born 5 months before, without heart symptoms	R.
67	23	10	2 + 1 D.	0	Mitral stenosis and regurgitation, acute rheumatism	"	"	Last child 14 months ago. Has never had cardiac symptoms since pericarditis at 13 years	R.
68	25	10	2	0	Mitral stenosis and regurgitation, acute rheumatism	"	"	Pregnancies natural	R.
69	25	20	2	0	Mitral stenosis and regurgitation, acute rheumatism	"	"	"	R.
70	27	Child-hood	6	1	Mitral stenosis, acute rheumatism	"	"	Miscarriage 1 month ago; no cardiac symptoms	R.
71	28	14	1	0	Mitral stenosis and regurgitation, aortic stenosis and regurgitation	Angina (1 year)	"	Child born without trouble	R.
72	30	7	3	—	Mitral stenosis, acute rheumatism (3th attack)	Rheumatism	"	Pregnancies natural	R.
73	30	None	0	2	Mitral stenosis, general debility for 2 years	Debility	"	Last miscarriage 8 years ago	R.
74	31	Child-hood	3	1	Mitral stenosis and regurgitation, pneumonia	Pneumonic	"	Abortion 2 months ago, pneumonia followed; there were no cardiac symptoms	R.
75	35	5	5	0	Mitral stenosis and regurgitation, aortic stenosis and regurgitation, acute rheumatism (4th attack)	Rheumatism	"	Was known to have bruits at 12; has never had heart failure; last child 7 months ago	R.
76	36	15	4	—	Mitral stenosis and regurgitation, pleurisy	Pleuritic	"	Pregnancies natural	R.
77	36	9	3	—	Mitral stenosis, diabetes mellitus	Diabetic	"	"	R.
78	37	Child-hood	5	0	Mitral stenosis, movable kidney	Pain in loin	"	"	R.

Case number.	Age.	Age at which rheumatism or chorea.	Number of children.	Number of miscarriages.	Main diagnosis.	Symptoms for which admitted.	Duration of cardiac failure.	Details.	Result.
79	37	None	7	1	Mitral stenosis, hemiplegia (sudden embolism)	Hemiplegia	None	Last child 2 years ago without trouble	R.
80	37	13	1	0	Mitral stenosis, diabetes mellitus	Diabetic	"	Child born 5 years ago	R.
81	37	15	1	—	Mitral stenosis, acute rheumatism	Rheumatism	"	Pregnancy natural	R.
82	40	None	2	—	Mitral stenosis, carcinoma of liver	Malignant	"	Last pregnancy 3 years ago	Worse
83	40	"	3	0	Mitral stenosis and regurgitation, chronic osteoarthritis	Chronic joints	"	The chronic joint trouble (? septic synovitis) dated from a labour 2 years before; there had been no cardiac symptoms	R.
84	41	15	5	—	Mitral stenosis and regurgitation, acute rheumatism and simple stricture of oesophagus	Dysphagia	"	There had been no heart symptoms; she came in for simple stricture of oesophagus, and developed acute rheumatism in the ward	R.
85	44	14	7	—	Mitral stenosis, cerebral embolism, acute rheumatism	Hemiplegia	"	Last pregnancy was 6 years ago; there had been no cardiac symptoms; the hemiplegia was recent	R.
86	47	Childhood	4	—	Mitral stenosis, phthisis	Acute abdominal pain	"	Pregnancies uneventful; there had never been cardiac symptoms	R.
87	51	None	10	—	Mitral stenosis (old and fibrous) found p. m., admitted for perforated gastric ulcer, the mitral disease was unsuspected	Abdominal	"	Ditto	D.
88	56	18	8	2	Mitral stenosis, hysterical epilepsy	Hysterical	"	Ditto	R.

89	23	14	1	—	Mitral stenosis, lobar pneumonia	Pneumonic	None	R.
90	30	20	3	1	Mitral stenosis and regurgitation, ascites	Palpitations and cedema	3 months	R.
91	31	16	5	0	Mitral stenosis and regurgitation, big liver, ascites, double pleural effusion	Dyspnoea, ascites	6 months acute, 15 yrs. chronic	R.
92	33	5	3	—	Mitral stenosis and regurgitation	Dyspnoea and precordial pain	Acute	R.
93	41	12	4	2	Ditto	Ascites and bronchitis	7 weeks	R.
94	41	16	4	—	Mitral stenosis and regurgitation, aortic regurgitation	Dropsy	Recent	D.
95	42	Childhood	8	—	Mitral stenosis and regurgitation, anasarca	Dyspnoea and dropsy	8 months	R.
96	43	None	1	—	Mitral stenosis	Dyspnoea	Acute lately	R.
97	69	19	1	—	Mitral stenosis and regurgitation	Precordial pain and dyspnoea	Recent	R.

Heart disease known since 14; no cardiac symptoms
 No heart symptoms till 3 months ago; bruits known before marriage; pregnancies uneventful
 Has had dyspnoea since she was 16, when she was known to have heart disease; she married in spite of this, and has had 5 pregnancies without increase in symptoms; two of the children were short of full term, but lived; the acute symptoms definitely did not date from the last pregnancy
 Was known to have heart disease at 13. The pregnancies caused no cardiac symptoms
 Has had dyspnoea and palpitations off and on since 13; she had no increase of symptoms during child-bearing
 Has had dyspnoea off and on since 16; she had no increase of symptoms during child-bearing; she was married at 19
 The last pregnancy was 3 years ago. She was married at 22. The bruits had been known to exist for 10 years. She bore her children without cardiac symptoms, but transient hemiplegia occurred 3 days after last labour, 3 years ago
 She has had dyspnoea on exertion as long as she can remember; the child was born 25 years ago without any trouble
 Cardiac bruits known since 19

Case number.	Age.	Age at which rheumatism or chorea.	Number of children.	Number of miscarriages.	Main diagnosis.	Symptoms for which admitted.	Duration of cardiac failure.	Details.	Result.
98	24	8	1	0	Mitral stenosis and regurgitation, pericarditis, ascites	Pericarditic	Recent	The only pregnancy was 5 years ago, without trouble	D.
99	28	8	1	—	Mitral stenosis and regurgitation, infective endocarditis	Dyspnoea and weakness Edema and dyspnoea	Gradual onset for 1 year 2 months	The only pregnancy was 9 years ago, without trouble	D.
100	28	None	1	3	Mitral stenosis and regurgitation, infective endocarditis, thromboses			Married 8 years, no recent pregnancy	D.
101	28	"	2	—	Mitral stenosis and regurgitation, aortic stenosis and regurgitation, ulcerative endocarditis	Hemiplegia, acute 3 months ago, vomiting	Diagnosed as gastric ulcer 3 months ago, no cardiac symptoms Recent	Pregnancies uneventful	D.
102	32	10	3	—	Mitral stenosis and regurgitation, infective endocarditis	Pyrexia and joint pains		"	D.
103	32	Childhood	5	—	Mitral stenosis and regurgitation, anasarca	Dropsy and dyspnoea	Getting worse for 1 year 11 months	Married at 16; last labour some years before admission, without difficulty	D.
104	33	None	2	0	Mitral stenosis and regurgitation, big liver, etc., infective endocarditis	Dyspnoea		Last pregnancy was 3 years ago, without trouble. The mitral stenosis found p. m. was extreme	D.
105	35	"	7	—	Mitral stenosis, pericarditis, pneumonia, the mitral stenosis was unsuspected, but was found p. m.	Pneumonic	Acute	No cardiac symptoms; pregnancies uneventful	D.

Case number.	Age.	Age at which rheumatism or chorea.	Number of children.	Number of miscarriages.	Main diagnosis.	Symptoms for which admitted.	Duration of cardiac failure.	Details.	Result.
118	43	14	1	—	Mitral stenosis and regurgitation, aortic stenosis and regurgitation, infective endocarditis, adherent pericardium	Rheumatic pains	Recent	The child is 19 years old	D.
119	43	None	4	Sev- eral	Mitral stenosis, tricuspid stenosis	Hemiplegia	Sudden embolism	Pregnancies uneventful	D.
120	44	"	13	—	Mitral stenosis and regurgitation, aortic regurgitation, adherent pericardium, infarcts in kidney and spleen	Dyspnoea	Sudden onset 3 months ago	"	D.
121	44	7	2	—	Mitral stenosis and regurgitation, aortic regurgitation, tricuspid stenosis	"	2 years, on and off	Pregnancies uneventful, early in married life	D.
122	44	20	3	—	Mitral stenosis and regurgitation, adherent pericardium	Palpitations	3 months	Last child 8 years ago	D.
123	45	Girl- hood	6	0	Mitral stenosis and regurgitation, extreme cyanosis, oedema	Dyspnoea and oedema	12 years off and on, present attack began 1 month ago	Last pregnancy preceded first cardiac symptoms by years	D.
124	46	Child- hood	7	—	Mitral stenosis and regurgitation, aortic disease, infective endocarditis, big liver, etc.	Oedema and dyspnoea	1 year	Husband has been dead over 6 years; pregnancies uneventful	D.

125	49	None	7	—	Mitral stenosis and regurgitation, big liver, etc.	Ditto	5 years	Pregnancies uneventful	D.
126	49	Childhood	8+ 1 D.	0	Mitral stenosis, ascites, infective endocarditis	Ditto	8 months	Last child 11 years ago	D.
127	49	None	5	—	Mitral stenosis, thrombosis renal and radial arteries and aorta	Acute pains	Acute	Pregnancies uneventful	D.
128	51	"	14	—	Mitral stenosis and regurgitation, adherent pericardium	Acute pain in chest	"	Pregnancies uneventful; the mitral stenosis was extreme	D.
129	52	12	2	—	Mitral stenosis and regurgitation, aortic stenosis and regurgitation, big liver, ascites, pleural effusions	Dyspnoea and oedema	Recent	Pregnancies uneventful	D.
130	52	None	11	2	Mitral stenosis, tricuspid regurgitation, ascites	Anasarca	6 weeks	"	D.
131	57	18	9	2	Mitral stenosis, oedema, etc.	Cough, oedema of legs Anasarca	On and off 7 years 2 weeks	Pregnancies uneventful; on one occasion twins	D.
132	58	None	7+ 3 D.	—	Mitral stenosis and regurgitation, ascites, etc.	Anasarca	1 year	Pregnancies uneventful	D.
133	61	"	0	4	Mitral stenosis, quite unexpected, but found p. m. There had been no bruit, kidneys healthy	Dyspnoea and weakness, oedema	2 years, recent	"	D.
134	61	14	2	3	Mitral stenosis, aortic stenosis, tricuspid stenosis, pulmonary stenosis	Dyspnoea and weakness	2 years	"	D.
135	71	None	11	—	Mitral stenosis found p. m., no bruit during life, kidneys sound	Oedema and bronchitis	5 months	"	D.

B *Those who had been Pregnant, and did relate Cardiac Symptoms to a Pregnancy or Labour.*

Case number.	Age.	Age at which rheumatism or chorea.	Number of children.	Number of miscarriages.	Main diagnosis.	Symptoms for which admitted.	Duration of cardiac failure.	Details.	Result.
136	24	None	2	1	Mitral stenosis and regurgitation, ? tricuspid stenosis	Palpitations	4 months	We are not certain of the relation, but suspect it	R.
137	26	"	4	2	Mitral stenosis and regurgitation, ascites, etc.	Ascites	1½ years	Married 9 years. We suspect the condition was made worse by child-bearing	R.
138	33	"	6	—	Mitral stenosis, bronchitis	Bronchitis	16 years off and on	She dates her trouble from small-pox at 16. She had her first child 12 years ago, the last 9 days ago. She has had bronchitis and dyspnoea badly with each pregnancy, recovering between. The present attack has been her worst, and dates from soon after labour, 9 days ago	R.
139	37	15	12	—	Mitral stenosis and regurgitation	Dyspnoea	2 months	Eleven pregnancies were uneventful; dyspnoea came on 10 days after her twelfth labour, 2 months ago	R.
140	38	None	4	2	Mitral stenosis and regurgitation, anasarca	Œdema and dyspnoea	4 years	She had no symptoms of heart trouble until just after the last labour, an 8 months living child, 4 years ago	R.
141	39	17	4	3	Mitral stenosis and regurgitation, big liver, etc.	Ditto	6 years	We do not know for certain the relation, but suspect heart trouble was made worse by pregnancies; she had been married 11 years	R.
142	39	None	6	2	Mitral stenosis, bronchitis	Cough	—	She had bad bronchitis each time she was carrying; no œdema	R.
143	40	14	6	—	Mitral stenosis, pulmonary regurgitation,	Œdema	11 years off and on	She dates her cardiac symptoms from soon after the birth of her second	R.

144	46	18	11	—	ascites, etc.		Palpitations, etc.	4 years	child, 11 years ago; she has borne 4 children since, each time with but slight exacerbation of her symptoms	R.
145	47	None	3	—	Mitral stenosis and regurgitation, pleurisy		Pleurisy	Heart trouble on and off 9 years	She was quite well until 4 years ago, having borne 10 children without trouble; she dates her symptoms from shortly after the birth of her eleventh child (a living 7 months infant), 4 years ago	R.
146	26	13	2	—	Mitral stenosis and regurgitation, aortic stenosis and regurgitation		Dyspnoea	2 months acute	Last child 9 years ago; the two previous gave no trouble	R.
147	25	None	2	0	Mitral stenosis and regurgitation, pleuritic effusion, old hemiplegia		"	On and off ever since a child	Was quite well till 3 months after birth of first child, when she had acute dyspnoea; the second pregnancy was uneventful except for persistent dyspnoea, which became acutely worse again some while after labour	R.
148	33	16	.6	—	Mitral stenosis, tricuspid regurgitation		Edema and precordial pain	8 weeks	The last pregnancy was 2 years ago; there was no trouble with the previous child, nor indeed with the last, but the dyspnoea got gradually worse and worse after the labour; she was still alive 3 years later	R.
149	21	None	1	0	Infective endocarditis on old mitral stenosis		Hæmoptysis, and splenic pain	6 weeks	No trouble with first 5 pregnancies, though heart disease was known from 16; 3 weeks before sixth child was born oedema of the legs began; after labour this went on to anasarca; she recovered	Worse
150	23	12	4	—	Mitral stenosis and regurgitation, ascites, etc.		Dyspnoea	3 years, acute 3 weeks	No trouble with pregnancy or labour; is now 5 months pregnant; went out, still pregnant, against advice	R.
									The 4 children were born without trouble, but 3 weeks ago, 2 months after last labour, acute dyspnoea set in	

Case number.	Age.	Age at which rheumatism or chorea.	Number of children.	Number of miscarriages.	Main diagnosis.	Symptoms for which admitted.	Duration of cardiac failure.	Details.	Result.
151	24	Girl- hood	1	—	Mitral stenosis, bron- chitis	Cough; no oedema	Recent	Was pregnant 5½ months on admission; she got much better and went out; relapsed, came in again, recovered, went out again, and went to term without further trouble	R.
152	24	None	0	0	Mitral stenosis	Dyspnoea and hæmoptysis	3 months	Was pregnant 5 months on first admission; got better on treatment, went out, relapsed, came in again, got better, went out again still pregnant	R.
153	24	16	1 d.	—	Mitral stenosis, aortic regurgitation	Dyspnoea (not bad)	Years	Married 12 months. Had been in and out of hospital seven times for heart disease before marriage. She was in bed in hospital 203 days; was then delivered of a dead 8-months fœtus, and went out 14 days after labour pretty well	R.
154	27	17	0	1	Mitral stenosis, ascites, tapped	Ascites	1½ years	She has been married 2 years. Ascites developed during first pregnancy and caused miscarriage. She has had oedema and ascites on and off ever since	R.
155	27	None	4 + 1 d.	—	Mitral stenosis	Dyspnoea, hæmoptysis	14 months, 6 months	She bore 3 children without trouble. The fourth was 4 years ago; 5 months before this labour she had a cerebral embolism with hemiplegia. She got better of this, and had no heart trouble till 14 months ago, when dyspnoea began; 7½ months ago she became pregnant again, and 1½ months later hæmoptysis started. Cough increased during pregnancy.	R.

156	28	16	4	—	Mitral stenosis and regurgitation, ascites, pleuritic effusion	Ascites	5 months	but she went almost to term, and had a living child weighing 6 lb. 8 oz., natural delivery. She went out fairly well	R.
157	28	None	1 + 1 d.	—	Mitral stenosis and regurgitation, ascites	Dyspnoea and ascites	6 months	The first 3 labours were natural. Soon after the fourth child was born cardiac trouble began	R.
158	29	None	4	2	Mitral stenosis, aortic regurgitation, pleuritic effusion	Hæmoptysis, severe dyspnoea	3 years off and on, 1 month	She had no trouble with first pregnancy, 6 years ago. Soon after the second, 6 months ago, ascites began and increased	R.
159	30	Childhood	2	0	Mitral stenosis and regurgitation, tricuspid regurgitation, etc.	Severe dyspnoea	11 months	The third full-term child was 3 years ago; she dates hæmoptysis from then. After that she had two miscarriages; a month ago she was delivered of her fourth full-term child, living, and has been in bed with severe dyspnoea since	R.
160	31	None	3	0	Mitral stenosis and regurgitation, cedema	Bronchitis, cedema	Some years off and on, 20 months	There was no trouble with the first child; the second was born 11 months ago, and following labour the dyspnoea set in	Worse
161	32	Girlhood	5	0	Mitral regurgitation	Hæmoptysis	Recent	Was quite well till after first labour; bronchitis then set in, and recurred with each of the two pregnancies; the last labour was 20 months ago; cedema set in after this last labour. Infective endocarditis was suspected on last admission, on account of pyrexia; she went home worse	R.
								She was in hospital at 18 for palpitations and dyspnoea. She married subsequently, and had 4 children without trouble. When 6 months pregnant of fifth child she had sudden hæmoptysis, lasting 4 days. There was no other cardiac trouble; she only lay up 4 days; she went to term naturally	

Case number.	Age.	Age at which rheumatism or chorea.	Number of children.	Number of miscarriages.	Main diagnosis.	Symptoms for which admitted.	Duration of cardiac failure.	Details.	Result.
162	33	None	4	—	Mitral stenosis, bronchitis	Dyspnoea and bronchitis	8 months, worse 1 week	Three pregnancies gave no trouble; early in the fourth dyspnoea and hæmoptysis set in; she went to term, and the child was born alive; the dyspnoea got worse after labour; she came to hospital for relief and recovered with rest in bed	R.
163	33	Childhood	7	1	Mitral stenosis	Dyspnoea	Many years	The first four children caused no heart symptoms; with fifth and sixth there was dyspnoea. She is now pregnant 7 months, having had hæmoptysis for 7 months; cedema set in at 7 months, and got worse to term. The child was born living naturally; there was a bad attack of dyspnoea on fourth day after labour; the mother responded to treatment, and went out moderately well	R.
164	34	20	7	1	Mitral stenosis and regurgitation, infarcts in spleen and lungs	Cedema and ascites	4 months	She dates her heart failure directly to her miscarriage 4 months ago, when 6 months pregnant. There was no trouble with any of the previous 7 children	D.
165	34	Childhood	2	0	Mitral stenosis, pleurisy	Pleurisy	None	She came in with a week's history of pleuritic pain when pregnant nearly to term. A pleuritic effusion was found. Labour at term was natural	R.
166	36	None	2	0	Mitral stenosis, tricuspid stenosis	Dyspnoea	4 months	No trouble with pregnancy till fourth month, when acute dyspnoea set in. She had several attacks of dyspnoea, but went to term, and was delivered	R.

167	37	None	5	1	Mitral stenosis and regurgitation, ascites, etc.	Orthopnea and oedema	9 weeks	R.	of living twins (boys) naturally. Two weeks after labour there was another very acute attack of dyspnoea; the patient rallied rapidly, and went out apparently well She was quite well during five former pregnancies, but had a miscarriage 9 weeks ago, since when she has not been well She had no trouble at all with the first 12 children; when 4 months pregnant with the 13th she got very bad rheumatic fever, and was found to have signs of old mitral disease. She recovered and went out still pregnant
168	37	None	12	—	Mitral stenosis and regurgitation	Acute rheumatism	No real heart failure	R.	She got dyspnoeic during her first pregnancy, and has been bad with each subsequently. On two occasions labour was induced at the 8th month for heart failure, on one of which occasions p. p. h. was almost fatal. After her fourth child she was discharged "a wreck," but recovered at home, and bore two more children. The last of these was born without induction; it was a transverse presentation; version was performed; the mother and child both did well There was no trouble with first nine children; after the birth of the tenth, 14 months ago, dyspnoea set in, and has been getting worse and worse since
169	38	20	6	—	Ditto	Oedema and dyspnoea	Many years on and off	R.	No trouble with former labours. When pregnant for eighth time, and near to term, dyspnoea began, followed by easy labour and recovery. The child was dead
170	38	12	10	—	Ditto	Dyspnoea	14 months	R.	
171	41	16	5+	2	Aortic disease and mitral stenosis	"	Recent	R.	

Case number.	Age.	Age at which rheumatism or chorea.	Number of children.	Number of miscarriages.	Main diagnosis.	Symptoms for which admitted.	Duration of cardiac failure.	Details.	Result.
172	43	18	13	—	Mitral stenosis and regurgitation, aortic stenosis and regurgitation	Œdema.	5 months	12 pregnancies were uneventful; with the 13th cardiac symptoms began; œdema set in 2 months after labour, and grew worse. She recovered with rest in bed	R.
173	41	None	7	—	Mitral stenosis and regurgitation	Anginal pain	14 years	3 pregnancies were uneventful; after the fourth labour anginal attacks began. Notwithstanding these, she bore three more living children, the last six years ago. She is a chronic invalid.	Very ill.
174	25	None	1	—	Mitral stenosis, thromboses, anasarca	Dyspnoea	14 days	The child was born living 14 days ago; there were no symptoms till after labour	D.
175	38	"	8	—	Mitral stenosis and regurgitation, calcareous vegetations	"	11 weeks	Was quite well until after last confinement, 11 weeks ago; the first 7 pregnancies were uneventful	D.
176	31	"	8	—	Mitral stenosis, pleuritic effusion	Anasarca, precordial pain, dyspnoea	7 weeks + many years on and off	She had cardiac symptoms shortly after second pregnancy, and was short of breath through all the subsequent ones; the first was natural, the last was 7 weeks ago	D.
177	31	"	5	1	Mitral stenosis and regurgitation, aortic stenosis, infarcts in lungs	Dyspnoea and œdema	1 year	She came in pregnant and got better under treatment; she went out and went to term naturally; she came in again a few weeks afterwards. She dated her heart symptoms to the miscarriage 1 year ago	D.

178	30	17	1	0	Mitral stenosis, tricuspid stenosis, aortic stenosis, infarcts in lungs, gastric ulcer	Anasarca, dyspnoea, and hæmatemesis	Some months	The cardiac symptoms came on early in the only pregnancy, but she rested and went to term; the child was small, living; she collapsed 10 days after labour, a few days before admission; she got worse and worse, and died	D.
179	25	None	2	2	Mitral stenosis, infective endocarditis, various infarcts	Edema and weakness, and acute hemiplegia	Recent + some years	The first labour at term was natural; then followed two miscarriages, and there were cardiac symptoms with each; the last labour at term was 10 months ago, without much trouble, but the patient has never been well since; the progress was downhill continuously	D.
180	23	"	3	1	Ditto	Chorea	Recent	There had been no previous chorea; the three children were born without trouble. When pregnant fourth time, she developed chorea at sixth month and aborted 21 days afterwards; she went rapidly downhill and died 23 days after the abortion	D.
181	31	12	5	—	Mitral stenosis and regurgitation, adherent pericardium, ascites, etc.	Cough Edema	9 years 2 years	The first 4 children were born without trouble; the fifth was born alive at term 3 months ago naturally; edema of legs and ascites came on one week after labour; the patient went rapidly downhill	D.
182	20	14	1	0	Mitral stenosis and regurgitation, infective endocarditis, pericarditis	Edema	2½ years	Symptoms of heart failure came on early during the only pregnancy, 2½ years ago; the cardiac symptoms were so bad that labour was induced at the eighth month; the child lived. The mother recovered a little, but was a chronic invalid, and finally developed malignant endocarditis	D.

Case number.	Age.	Age at which rheumatism or chorea.	Number of children.	Number of miscarriages.	Main diagnosis.	Symptoms for which admitted.	Duration of cardiac failure.	Details.	Result.
183	28	None	4	0	Mitral stenosis, tricuspid regurgitation	Dyspnoea	Some months	She "had never been ill in her life" until, when 4 months pregnant of the fourth child, symptoms of dyspnoea and cough came on; after rest and digitalis in hospital she got better and went home. She returned at term, and had a living child easily; the mother did well at first, but a few days after getting up she developed further heart symptoms, and rapidly went downhill and died	D.
184	24	16	1	—	Mitral stenosis and regurgitation, bronchitis	Dyspnoea and oedema	18 months	Heart failure began during the pregnancy, but acute symptoms did not arise until a living child had been born at term. Since then she had been in and out of hospital 5 times in a year, never really recovering compensation	D.
185	40	None	4	4	Mitral stenosis, infarcts in kidneys	Dyspnoea	5 months	She had always been well, except that 10 years ago she was in hospital for albuminuria during pregnancy. Four labours and 3 miscarriages were without cardiac symptoms; the latter date from a miscarriage at the 3rd month, 5 months ago	D.
186	28	Childhood	1	—	Mitral stenosis, tricuspid stenosis, aortic regurgitation	General failure	2 years	She was quite well till the child was born, 2 years ago; heart failure set in soon after labour, and she has never been well since	D.
187	28	None	1	—	Mitral stenosis, hemiplegia, infarcts, tricuspid vegetations	Palpitations and hæmoptysis	5 years	Palpitations and hæmoptysis have recurred during the last five years. The only child was born living at the	D.

188	32	17	2	—	Mitral stenosis and regurgitation, hemiplegia	Cedema	3 years on and off	D.	7th month, 8 months ago, and the cardiac symptoms became much worse. She has gone downhill ever since. The first child was born normally. The symptoms date from soon after the birth of the second child, 3 years ago
189	38	6	1	—	Mitral stenosis, infective endocarditis, pleuritic effusion, various infarcts	Dyspnoea and hæmoptysis	7 months	D.	The child was born naturally 9 months ago. Two months later dyspnoea and hæmoptysis set in; the heart symptoms went from bad to worse
190	41	8	6+ 1 D.	1	Mitral stenosis and regurgitation, infective endocarditis	Cedema, dyspnoea, acute	9 months 2 weeks	D.	There was no trouble till the last child was born, 2 years ago. Soon after she had hemiplegia. No other cardiac symptoms followed until 9 months ago, when cedema appeared; she became acutely dyspnoeic 2 weeks ago and died in a few weeks
191	43	8	2	—	Mitral stenosis and regurgitation, vegetations, cedema, hæmoptysis	Dyspnoea, cedema	1½ years 1 month	D.	The first child brought no heart trouble. Three months after the birth of the second, 1½ years ago, the patient became dyspnoeic. She was able to do her work until 1 month ago, when cedema came on, and she died soon after admission. It is doubtful if this can really be attributed to the pregnancy
192	48	Girlhood	8	4	Mitral stenosis and regurgitation, general heart failure	Dyspnoea	10 years	D.	The patient directly dates symptoms to a labour 10 years ago. She has since been pregnant 3 times. The eldest child is 25, the youngest 6. She has never been well since the last was born, though she has done her work on and off till recently
193	25	18	—	—	Mitral stenosis and regurgitation	Rheumatism	None	R.	<i>C. Cases Married, but never Pregnant.</i> Married 3 years.

Case number.	Age.	Age at which rheumatism or chorea.	Number of children.	Number of miscarriages.	Main diagnosis.	Symptoms for which admitted.	Duration of cardiac failure.	Details.	Result.
194	26	None	—	—	Mitral stenosis and regurgitation	Dyspnoea and precordial pain	2 years	Married recently. Heart troubles started before marriage	Worse
195	26	Girlhood	—	—	Mitral stenosis, bronchitis	Œdema and cough	5 weeks	—	D.
196	29	None	—	—	Mitral stenosis, tricuspid regurgitation	Dyspnoea and weakness	6 years	Married 9 years	D.
197	31	16	—	—	Mitral stenosis and regurgitation, bronchitis	Cough and precordial pain	2 months	Married 11 years	R.
198	34	None	—	—	Mitral stenosis and regurgitation, pulmonary regurgitation, ascites, etc.	Œdema and ascites	"	Married 8 years, and has been out of health on and off ever since	R.
199	34	"	—	—	Mitral stenosis and regurgitation, aortic stenosis and regurgitation	Dyspnoea and œdema	4 months	—	R.
200	35	16	—	—	Mitral stenosis, general failure	Dyspnoea	18 months	Has been in Guy's Hospital more than a dozen times. She recovers quickly, but soon relapses. She is a widow. Had cerebral embolism 9 years ago.	R.
201	36	7	—	—	Mitral stenosis, anasarca	Dyspnoea and ascites	1 year	Married 18 years	D.
202	36	None	—	—	Mitral stenosis and regurgitation, tricuspid regurgitation	Orthopnoea and œdema	17 years	Married 8 years. A chronic hospital inmate	R.
203	39	"	—	—	Mitral stenosis, epithelioma of œsophagus	Dysphagia	None	Married 9 years. Mitral stenosis, unsuspected, found p. m.	D.
204	41	4	—	—	Mitral stenosis and regurgitation, double aortic disease	Dyspnoea	Months	—	D.
205	55	12	—	—	Mitral stenosis, hæmatemesis	Dyspnoea and cyanosis	28 years on and off	—	D.

D. Unmarried cases.

206	20	6	—	Mitral stenosis	Dyspnea, hæmoptysis	2 years	—	R.
207	20	None	—	Mitral stenosis, aortic stenosis	Dyspnea and palpitations	2 months	—	R.
208	20	Child-	—	Mitral stenosis	Dyspnea	3 years	—	R.
209	21	hood	—	Mitral stenosis, acute rheumatism	Precordial pain	None	—	R.
210	21	19	—	Mitral stenosis and regurgitation, acute rheumatism	Dyspnea	2 years on and off	Hemiplegia due to cerebral embolism occurred just before admission	R.
211	21	12	—	Mitral stenosis and regurgitation	Dyspnea	Acute	—	R.
212	21	Girl- hood	—	Mitral stenosis and regurgitation, aortic stenosis, acute rheumatism	Precordial pain	3 months	—	R.
213	21	12	—	Mitral stenosis and bronchitis	Cough and dyspnea	7 years	—	R.
214	21	None	—	Mitral stenosis and regurgitation, aortic stenosis and regurgitation	Precordial pain	Acute	—	R.
215	21	10	—	Mitral stenosis and regurgitation, bronchitis	Cough and pain in chest	2 weeks	—	R.
216	21	10	—	Mitral stenosis and regurgitation, anasarca	Dyspnea	Recent	—	R.
217	21	7	—	Mitral stenosis and regurgitation	Pain in side, cedema	"	—	R.
218	22	14	—	Mitral stenosis and regurgitation, paracentesis abdominis	Precordial pain, ascites	1 year	—	R.
219	22	10	—	Mitral stenosis and regurgitation	Dyspnea	Recent	—	R.
220	22	10	—	Mitral stenosis and regurgitation, large liver, etc.	Edema	1 month	—	R.

Case number.	Age.	Age at which rheumatism or chorea.	Number of children.	Number of miscarriages.	Main diagnosis.	Symptoms for which admitted.	Duration of cardiac failure.	Details.	Result.
221	22	None	—	—	Mitral stenosis and re- gurgitation, bron- chitis	Dyspnoea and oedema	6 months	Was often admitted afterwards. A chronic invalid	R.
222	22	11	—	—	Mitral stenosis and re- gurgitation	Acute rheumatism	None	—	R.
223	23	11	—	—	Mitral stenosis and re- gurgitation, infective endocarditis	Hæmaturia	Recent	Went home to die	Worse
224	23	12	—	—	Mitral stenosis, epi- lepsy	Fits	None	—	R.
225	23	None	—	—	Mitral stenosis and re- gurgitation, rheu- matic nodules	Weakness	Months	—	R.
226	23	Child- hood	—	—	Mitral stenosis, hæma- temesis	Hæmate- mesis	None	—	R.
227	23	14	—	—	Mitral stenosis and re- gurgitation	Oedema	5 months	—	R.
228	23	14	—	—	Ditto	Dyspnoea	Recent	—	R.
229	23	Child- hood	—	—	Mitral stenosis and re- gurgitation, aortic stenosis and regurgi- tation	"	4 years	—	R.
230	23	16	—	—	Mitral stenosis and re- gurgitation, peri- carditis	Dyspnoea	3 months	—	R.
231	23	None	—	—	Mitral stenosis and re- gurgitation, exoph- thalmic goitre, Ray- naud's disease	Nervousness	None	—	R.
232	23	16	—	—	Mitral stenosis and re- gurgitation, bron- chitis	Cough and dyspnoea	4 months	—	R.

233	24	8	—	—	Mitral stenosis and regurgitation, gastritis	Gastric pain and vomiting	None	—	R.
234	24	7	—	—	Mitral stenosis and regurgitation, acute rheumatism (3rd attack)	Rheumatism	"	—	R.
235	24	19	—	—	Mitral stenosis and regurgitation, gastritis	Gastric pain	"	—	R.
236	24	None	—	—	Mitral stenosis, ganglion on wrist	Ganglion	"	—	R.
237	24	9	—	—	Mitral stenosis and regurgitation, nutmeg liver	Dyspnoea and cedema	Years	—	R.
238	24	16	—	—	Mitral stenosis and regurgitation, aortic stenosis and regurgitation	Dyspnoea	"	—	R.
239	25	9	—	—	Mitral stenosis and regurgitation, ascites	"	2 months	—	R.
240	25	None	—	—	Mitral stenosis and regurgitation	Œdema	1 year	Palpitations for 7 years	R.
241	25	16	—	—	Ditto	Precordial pain and cedema	Recent	—	R.
242	25	None	—	—	Ditto	Palpitation	1 year	—	R.
243	25	"	—	—	Ditto	Dyspnoea and cedema	4 years	—	R.
244	26	20	—	—	Mitral stenosis and regurgitation, pleuritic effusion	Ditto	1 year	There was slight cerebral embolism 1 year ago	R.
245	26	None	—	—	Mitral stenosis and regurgitation, pericarditis	Ditto	10 months	—	R.
246	27	7	—	—	Mitral stenosis and regurgitation	Œdema	2 weeks	—	R.
247	27	12	—	—	Mitral stenosis and regurgitation, aortic regurgitation	Bad dyspnoea and cough	Years	Has been in and out of hospital nearly a dozen times	A wreck

Case number.	Age.	Age at which rheumatism or chorea.	Number of children.	Number of miscarriages.	Main diagnosis.	Symptoms for which admitted.	Duration of cardiac failure.	Details.	Result.
248	27	7	—	—	Mitral stenosis and regurgitation, aortic stenosis	Dyspnoea and palpitations	7 months	—	R.
249	28	10	—	—	Mitral stenosis and regurgitation	Edema	2 years	—	R.
250	28	16	—	—	Mitral stenosis, chronic osteoarthritis	Deformed joints	None	—	R.
251	28	12	—	—	Mitral stenosis and regurgitation, aortic stenosis and regurgitation	Pleuritic effusion	Acute	—	R.
252	28	Childhood	—	—	Mitral stenosis, tricuspid regurgitation	Dyspnoea and edema	1 year	—	R.
253	28	None	—	—	Mitral stenosis and regurgitation, cerebral embolism	Hemiplegia	None	—	R.
254	29	11	—	—	Mitral stenosis and regurgitation, aortic regurgitation, big liver	Orthopnoea	4 years	—	R.
255	30	10	—	—	Mitral stenosis and regurgitation, aortic regurgitation	Hæmoptysis	Recent	—	R.
256	30	6	—	—	Mitral stenosis	Precordial pain	4 years	—	R.
257	31	18	—	—	"	Hæmoptysis	None	—	R.
258	31	14	—	—	Mitral stenosis and regurgitation, aortic stenosis and regurgitation	Dyspnoea	1 year	—	R.
259	32	None	—	—	Mitral stenosis and regurgitation, big liver, etc., ascites	Orthopnoea	6 years	—	Worse

260	32	12	—	Mitral stenosis and regurgitation, pleurisy, typhoid fever	Enteric	None	—	R.
261	32	None	—	Mitral stenosis	Dyspnoea, Hemoptysis	6 months	—	R.
262	33	"	—	Mitral stenosis and regurgitation, bronchitis	Dyspnoea	1 year	—	R.
263	33	16	—	Mitral stenosis and regurgitation	Pleurisy	None	—	R.
264	34	7	—	Mitral stenosis, transverse myelitis	Dyspnoea	Years	Known to have had heart disease at 15.	R.
265	34	None	—	Mitral stenosis, carcinoma of breast	Paraplegia	None		R.
266	35	"	—	Mitral stenosis, carcinoma of breast	Dyspnoea	11 years		R.
267	35	5	—	Mitral stenosis, appendicitis	Appendicular	None	—	R.
268	35	16	—	Mitral stenosis and regurgitation, tricuspid regurgitation	Dyspnoea	9 years	Known to have had heart disease at 14.	R.
269	35	Childhood	—	Mitral stenosis and regurgitation, aortic regurgitation	"	3 years		R.
270	35	None	—	Mitral stenosis	Precordial pain	8 months		R.
271	36	"	—	"	Cough and weakness	1 year	—	R.
272	37	"	—	Mitral stenosis, acute rheumatism, mania	Insanity	None	—	R.
273	37	16	—	Mitral stenosis, cerebral embolism	Hemiplegia	6 years	—	R.
274	38	Girlhood	—	Mitral stenosis, gastric ulcer	Hematemesis	None	—	R.
275	39	20	—	Mitral stenosis, mad with delusions	Hemoptysis	11 years, on and off	—	R.
276	40	None	—	Mitral stenosis, aortic regurgitation	Dyspnoea	6 weeks	—	R.
277	40	19	—	Mitral stenosis, tricuspid regurgitation, bronchitis	Dyspnoea and cough	3 years	—	R.

Case number.	Age.	Age at which rheumatism or chorea.	Number of children.	Number of miscarriages.	Main diagnosis.	Symptoms for which admitted.	Duration of cardiac failure.	Details.	Result.
278	40	None	—	—	Mitral stenosis, pelvic tumour, no operation	Dyspnoea	Many years	—	R.
279	43	"	—	—	Mitral stenosis and regurgitation, aortic stenosis	"	Years	—	R.
280	45	Childhood	—	—	Mitral stenosis and regurgitation	Dyspnoea and oedema	4 months	—	R.
281	47	20	—	—	Mitral stenosis and regurgitation, big liver, etc.	Dyspnoea and pain	Years	—	R.
282	48	None	—	—	Mitral stenosis and regurgitation, big heart, bronchitis	Ditto	1 year	—	R.
283	60	"	—	—	Mitral stenosis and regurgitation	Dyspnoea and cough	1 month	—	R.
284	21	None	—	—	Mitral stenosis and regurgitation, aortic regurgitation	Dyspnoea	1½ years	—	D.
285	23	9	—	—	Mitral stenosis, pericarditis	"	1 year	—	D.
286	23	None	—	—	Mitral stenosis, infective endocarditis, infarcts	Malaise	Recent	—	D.
287	23	16	—	—	Mitral stenosis and regurgitation, acute endocarditis	Dyspnoea	7 years	—	D.
288	23	None	—	—	Mitral stenosis, pericarditis, infective endocarditis	Dyspnoea and pain	4 months	—	D.
289	24	12	—	—	Mitral stenosis and regurgitation, aortic stenosis and regurgitation	Angina pectoris	6 years	—	D.

290	26	None	—	—	Mitral stenosis (old), infective endocarditis	Dyspnoea	2 years	—	D.
291	26	"	—	—	Mitral stenosis, pericarditis, pleurisy, exophthalmic goitre	Joint pains	None	—	D.
292	28	Childhood	—	—	Mitral stenosis, tricuspid stenosis, dropsy	Dropsy	3 years	—	D.
293	29	15	—	—	Mitral stenosis, pericarditis, pleuritic effusion, infarcts	Dyspnoea	Recent	—	D.
294	33	None	—	—	Mitral stenosis, infective endocarditis, infarcts	Sudden hemiplegia	"	—	D.
295	38	"	—	—	Mitral stenosis and regurgitation, big liver, infarcts	Dyspnoea	2 years	—	D.
296	40	Childhood	—	—	Mitral stenosis and regurgitation, adherent pericardium	"	Recent	—	D.
297	42	None	—	—	Mitral stenosis and regurgitation, tricuspid stenosis, anasarca	Dropsy	"	—	D.
298	44	"	—	—	Mitral stenosis, big liver, ascites, pericarditis, pleuritic effusion	"	"	—	D.
299	44	12	—	—	Mitral stenosis and regurgitation, aortic stenosis and regurgitation, adherent pericardium	Dyspnoea	Years	—	D.
300	41	19	—	—	Mitral stenosis and regurgitation, aortic stenosis and regurgitation, infective endocarditis	"	4 months	—	D.

LIFE AND MECHANISM.

Two Lectures delivered at the Physiological Laboratory, Guy's
Hospital, May 17th and 24th, 1906,

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Oxford.

LECTURE I.

GENTLEMEN,—As any branch of science advances it becomes necessary from time to time to examine, and if necessary modify or recast, the fundamental working hypotheses by means of which we seek to interpret the mass of concrete observation and experimental results constituting the matter of the science. To undertake such an examination in the case of physiology is, I am well aware, an extremely formidable task, and I should not venture upon it were I not convinced that a fresh examination is at present greatly required, and were not the subject one which has been constantly before my mind for many years.

To make this examination at all complete it will be necessary to survey the whole ground covered by physiology, and such a survey in the course of two lectures cannot be a detailed one. As my object is only to reach general conclusions, I shall endeavour to present only a general, or “low-power” view of the subject matter under discussion. For want of such a general view physiology has, I think, drifted into an unsatisfactory position, fundamental questions having been lost sight of through too exclusive concentration on investigations of detail.

It will be generally admitted that for the last fifty years the acknowledged working hypothesis of nearly all physiologists and biologists has been what may be designated as a mechanistic one. The object they have set before themselves has been to attain to physical and chemical explanations of the phenomena of life, and their working hypothesis has been that these phenomena are in ultimate analysis physical and chemical phenomena. Most biologists would, however, qualify this hypothesis with respect to consciousness, regarding this either as an accompaniment not influencing the physical and chemical changes, or as influencing only certain of them, but in any case as something on which physics and chemistry can throw no light, and which biology as such must ignore, leaving it to be dealt with by psychology.

THE VITALISTIC THEORY.

Previously to the middle of last century the common working hypothesis among physiologists was dualistic. It was generally believed that a great part of physiological phenomena could be explained on physical and chemical principles, but that there remained another and perhaps greater part which necessitated the assumption of a factor special to living beings—the so-called “vital force” or “vital principle.” This “vital force” was believed to interfere with and guide physical and chemical forces; and wherever the latter seemed insufficient to account for organic phenomena the balance of what could not be accounted for was attributed to the influence of vital force.

Before proceeding further it is necessary to examine carefully the causes of the almost universal abandonment of the theory of vital force, and the dualistic working hypothesis generally known as “vitalism.” These causes were, it seems to me, two in number. One was, broadly speaking, accidental and temporary; the other permanent in its influence.

The first of these causes was the fact that about the middle of last century many of the younger physiologists were convinced that they were on the point of being able to assign physical and chemical explanations to phenomena which had previously been referred to the influence of vital force. In describing his celebrated discoveries as to the animal cell, Schwann had in 1839

put forward the theory that cells are produced by a process akin to crystallisation. This was of course a direct attack on the prevailing vitalistic theory that growth is directed by vital force. Du Bois Reymond's observations on animal electricity, published in 1848, seemed to afford a prospect of an electrical explanation of the action of nerves; and Marshall Hall's theory of reflex action (1833) pointed towards a mechanistic theory of the central nervous system. Liebig's writings on chemical physiology gave a great stimulus to purely chemical explanations of the phenomena of animal metabolism, although he himself strongly supported vitalistic theories of muscular movement. Another heavy blow against vitalism was delivered when Meyer (1845) pointed out that there is no need to invoke vital force as a source of the energy of muscular movement, since the energy liberated by oxidation is sufficient to account for what appears in muscular movement. Ludwig's Text-book of Physiology, which appeared in 1852—1856, practically treated physiology as a branch of physics and chemistry, and in it were put forward his well-known mechanical theories of secretion, and other processes. The publication of Darwin's *Origin of Species* in 1859 gave a further great impetus to the mechanistic movement, not only in physiology, but in the whole of biology.

The second cause of the abandonment of vitalism was the inherent weakness of the vitalistic position. "Vital force" was conceived as something which interfered, now in the way of opposing, and now of strengthening, physical and chemical forces, the result of this interference being that the structure and functions of the living body are built up and maintained. It is evidently improper to call such an influence a "force," and the use of such an expression is evidence of confused thinking. The conception of force has no meaning except as an interaction between portions of matter, this interaction being, moreover, not capricious but perfectly regular. "Vital force" was conceived as acting upon matter from nothing, and acting capriciously.

If this objection were waived a further one remained. It was impossible to clearly isolate the influence of the supposed vital force; for in the cases where vital force was supposed to act

the physical and chemical conditions were always so complex that the limits of their influence were not definable. Apart from these complex physical and chemical conditions the supposed vital force never manifested itself, and all efforts to demonstrate within living organisms any source of energy other than the potential or kinetic energy introduced into the body from the environment have completely failed.

"Vital force" thus represented a confused conception, and was incapable of verification by any experiment. It was consequently useless as a means of explaining phenomena or suggesting definite paths of investigation, and was even blocking further progress. The mechanistic theory, on the other hand, suggested at every point clear and intelligible working hypotheses for further investigation, and thus appealed strongly to physiological investigators.

THE MECHANISTIC THEORY.

It is now necessary to examine the mechanistic theory itself. Impossible as it seems to return to vitalism, it is nevertheless very plain that a strong undercurrent in a vitalistic direction exists in the physiology of the present time, and has greatly increased in strength during the last thirty years.

The progress of investigation has shown that, so far from cell-formation being a simple physical and chemical process, each cell arises by a complex process of division from a pre-existing cell, and possesses from the beginning the apparent autonomy and complexity of metabolism of an independent living organism. When it was first realised that not the cell wall but the semi-fluid albuminous contents or "protoplasm" constituted the essential part of a cell, it was believed for a time that a definite physical basis of life had been reached. It gradually became evident, however, that the expression "protoplasm" has no more definite meaning than the word "flesh" as applied to the body substance generally. What at first appeared under the microscope as small masses of gelatinous substance turned out to be living organisms presenting on a small scale the essential complexities of function and structure which any independent living organism presents. Ludwig began his text-book of physiology with an account of

atoms, molecules, etc. ; later physiology must perforce start from the living cell.

When we turn to other sides of physiology a similar change of standpoint is very evident. What were fifty years ago believed to be simple physical and chemical processes have turned out to be only one side or another of the extremely complex activity constituting cell life. In Liebig's time the exchange of material in respiration was believed to be a comparatively simple chemical process of oxidation, dependent for its intensity on the supply of oxygen and of oxidisable material in the body fluids. The investigations of Pflüger and others have shown, however, that the oxidation is directly dependent on cell-activity. It does not, like ordinary chemical oxidation, increase or diminish in proportion to the varying supply of oxygen brought to the seat of oxidation, but is controlled by the living cells. The problem of oxidation in the living body is thus only one side of the general problem of cell-activity.

To take another instance, secretion, excretion, and absorption, have all been shown by the work of Ludwig, Heidenhain, and others to be not mere physical processes of filtration and diffusion, as was generally supposed fifty years ago, but to depend, like physiological oxidation, on cell life. If the secreting or absorbing cells die, or their activity is interfered with by a drug, or an insufficient supply of oxygen, or of anything else which is essential to cell life, secretion or absorption quickly stops.

To whatever department of physiology we may turn we are faced by the same fact—that all elementary physiological processes have turned out to be only different aspects of the same problem—that of cell nutrition or cell metabolism. The physico-chemical explanation of this has, on the other hand, made no progress whatsoever. Indeed, the further investigation is carried the more remote does the prospect appear of any physico-chemical analysis being ever reached. Had it turned out that there was no direct and immediate connection between the different "chemical" processes occurring in cells, or between the "chemical" and the "physical" processes, it would doubtless have been

possible to point to considerable progress towards physico-chemical explanation. We might have seen successful electrical theories of nervous and muscular action, filtration and diffusion theories of secretion and absorption, chemical theories of oxidation and other metabolic changes, crystallisation theories of tissue growth. But all attempts at such theories have been complete failures, so far; and the prospects of their success are unmistakably becoming less and less with every year.

It is also becoming increasingly evident that the relations between cell metabolism and cell environment are of enormous complexity. Physiological, pathological, and experimental embryological investigation are yearly furnishing further and further proofs that the metabolism of each cell in the body is dependent in the most intimate, complex, and far-reaching manner on its physiological relations to the other cells of the body. Thus the problem of the life of any single cell in an organism really involves the problem of the life of the whole of the cells. The analysis of the life of an organism into the activities of its constituent cells would thus seem to be by no means a simplification of the problem of physiology.

The failure of mechanistic theories to explain physiological processes would not by itself explain the constant tendency to relapse into the old vitalism. Alongside of this failure there is the evident fact that living organisms, unlike machines, have the capacity of preserving their normal structure and activities in spite of considerable vicissitudes in environment. They actively select from the environment and give or discharge into it the material and energy requisite to the fulfilment of this end, and thus possess what appears to be active autonomy. To explain this unity of aim in physiological processes the mind naturally tends to assume the existence of a special agency controlling physical and chemical processes in living organisms; and with the failure of physico-chemical explanations this tendency naturally grows in strength.

From the mechanistic side it may be urged that the apparent active autonomy of living organisms can be fully accounted for as the accumulated result of natural selection, acting through

countless generations; since organisms which do not actively preserve and reproduce their structure and activities will be eliminated in the struggle for existence. This contention is, however, open to a fatal objection. In order that natural selection may influence evolution it is necessary to assume that each organism actively maintains and reproduces its particular structure and activities. The co-ordinated activity and general fitness for its special function which are so conspicuous in each part of an organism, are relative only to the continued existence and reproduction of the organism as a whole. It is only on the presupposition that the organism as a whole is to be what it is that the structure or activity of any one part is adapted to its functions. If, to take an example, we presuppose that the metabolism of a warm-blooded animal is to be on the existing scale, then the lungs, alimentary canal, kidneys, circulatory system, etc., are admirably adapted to their purpose. But if we proceed to ask whether, considering only the fitness of the organism to survive in any form, such extravagant metabolism is needed, or whether any metabolism at all is desirable, and if not whether the lungs and other organs are not a superfluous source of weakness, we are engaging in an inquiry which to a biologist is barren and meaningless.

The principle of survival of the fittest would thus have no significance in the organic world but for the presupposition that the life of every organism is an actual struggle to realise in itself and its descendants a certain type of structure and physiological activity. In other words, the active autonomy of living organisms is itself one of the bases of the Darwinian theory, and hence cannot be explained as a result of natural selection.

It also follows that the direction in which natural selection influences evolution is determined, not merely by the blindly-acting influence of the environment, but by organisms themselves. The survival of any one of the endless small variations in structure or function on which natural selection acts must depend, in the long run, on whether or not this variation tends towards the fuller realisation of organic autonomy in the species concerned.

We must now push our examination of the mechanistic theory of life still further. It has already been pointed out that physiological investigation has shown more and more clearly that if life is a physico-chemical process, the process is one of enormous complexity and delicacy of adjustment. On the mechanistic theory this must depend on a corresponding complexity and delicacy of adjustment in the structure of living cells; and we must once and for all remove from our minds any idea that "protoplasm" is in any sense simple in its structure. Now we are met at once by the fact that the more complicated and definite we assume living structure to be, the more clearly does another difficulty in the mechanistic theory emerge—namely, that of explaining the phenomenon of reproduction. If we assume, as we are compelled to do on the mechanistic hypothesis, that each cell in the living body is an extremely complicated, and yet definite, mechanism, most delicately adjusted to its particular position and function, we have also to explain how this enormously complicated mechanical system can reproduce itself indefinitely in its offspring. The "mechanism" of reproduction must be more complicated than the mechanical system which it reproduces, for the process of reproduction has to be carried through numerous complicated stages before the final product, inconceivably complicated as it is, can be produced. All this mechanism must be supposed to be concentrated in the nucleus of the reproductive cell. But even this is by no means all; for the reproduction of the mechanism of reproduction has itself to be provided for, and its reproduction in turn, and so on indefinitely. The matter is still further complicated by the fact that in sexual reproduction two "mechanisms" of reproduction have to fuse together in order to produce the result.

It seems to me impossible to avoid the conclusion that when the facts of reproduction are fully and fairly faced the mechanistic theory of life must be abandoned as altogether inconsistent with the facts. It is evident that the difficulty is not avoided by assuming that the definiteness with which the ovum reproduces the complicated structure is due, not to the existence of a definite mechanism of reproduction in the nucleus of the ovum, but to the

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fact that its growth is determined in the right direction by the peculiar constitution of its environment. This assumption only shifts the difficulty from one place to another, and does not in any way help towards a mechanistic explanation.

Some writers on the subject of heredity have contented themselves with the idea that a sufficient mechanistic explanation of heredity is afforded by the hypothesis that the offspring is like the parent because each is developed from a portion of the same "germ plasma." They first treat "germ plasma" as if it were nothing but a structureless solution or jelly with the capacity of increasing in quantity at the expense of the environment. As one portion of such a jelly is qualitatively the same as another, it follows that each portion has the same potentialities, and is therefore equally capable or incapable of developing into a complete organism. But to explain the actual capacity which an ovum possesses of developing into a complicated organism it is necessary to ascribe to the concerned portion of the "germ plasma" an enormously complicated structure; and this the same writers proceed to do, quite regardless of the simple "plasma" from which they set out. Reasoning of such a kind need hardly be considered further. The "germ plasma" cannot be both a simple "plasma" and an enormously complicated structure. If it is the former, the development of an organism from it cannot be accounted for; if the latter its own formation cannot be accounted for.

The impossibility of explaining heredity is not, however, an isolated difficulty for the mechanistic theory of life, for in reality a similar difficulty is everywhere present in connection with physiological phenomena. It is met in a very definite form in connection with the facts of embryology and reproduction of lost parts. The accumulated experimental evidence of the last few years shows that when a cell, or group of cells, normally destined to develop into a certain part, such as one half, of the adult organism, is removed or displaced in an early embryo, a whole embryo will still be often formed. If, therefore, the developing embryo is nothing but a complicated mechanism, we are driven to the conclusion that it also contains additional developmental

mechanisms, capable of coming into action when the original mechanism is disturbed; and as the variety of disturbances which can be compensated for is indefinitely great, so the number of supplementary developmental mechanism must be indefinitely great. The reproduction of lost parts in an adult organism is a similar case. In the higher animals lost portions of the body are reproduced to a relatively limited extent, but in lower animals reproduction of lost parts is very common. It is impossible to believe that living cells possess a pre-arranged structure of such infinite complication that reproduction of lost parts can be not only brought about in one particular way, but also in an apparently infinite number of different ways, corresponding with the infinite number of different ways in which the injury recovered from is brought about.

Apart from accidental or experimental injuries, or developmental processes, the substance of the adult organism is constantly undergoing renewal in the ordinary processes of metabolic activity. In former times the structural "mechanisms" by which physiological processes were believed to be accomplished were sharply distinguished from the material with which they reacted, just as the parts of such a mechanism as a steam engine are sharply distinguished from the fuel, air, water, and steam which pass through it. It was believed, for instance, that secreting and absorbing organs act like mechanical filters; that chemical processes such as oxidation, with its accompanying heat-production, occur only in the interstices of the permanent structure of the body; that the nervous system is a permanent structure comparable to a system of telegraph wires; and that in fact everywhere structure exists apart from function, just as a machine exists apart from its actual working. Experimental investigation has, however, gradually shown that this belief is devoid of foundation. Not only do all the more important metabolic activities occur within living cells, and not outside them, but these processes seem to be continually proceeding, during both activity and apparent rest, the distinction between rest and activity being only a relative one—a difference in degree and not in kind. Thus a living animal cell, whether during apparent rest

or during activity, is continuously taking up oxygen and giving off carbonic acid; and if this process is suspended for even a short time the cell is rapidly disabled and its structure disorganised. It is also constantly taking up or giving off, or storing up within its substance, a variety of other substances, the number of which we have every reason to believe is very great, although only a few have been as yet completely identified. Such visible structure as can be made out in it varies according as one or another side of its metabolic activity becomes temporarily more predominant, as in the alternations of apparent rest and apparent activity; and to all appearances cell-structure is not an arrangement of fixed and permanent material comparable to the parts of a machine, but only the form taken by a constant metabolism or flow of material. We cannot arrest the metabolism and preserve the structure intact.

All this evidence points very clearly to the conclusion that the assumption of structural mechanisms in living cells cannot be made a basis for explaining the peculiarities of ordinary cell-activity any more than it can be made a basis for explaining the phenomena of reproductive activity. In the case of ordinary physiological activity the difficulty for the mechanistic theory is perhaps not so striking and evident at first sight, but is nevertheless of the same nature as in the case of reproductive activity. We cannot make structure the ultimate basis of explaining function. In admitting this, however, we admit the bankruptcy of the mechanistic theory, and this being so we must endeavour to find some better theory.

We have already seen that the old vitalism was wholly unsatisfactory. The expression "vital force" represented no clear conception—no positive working hypothesis. In one respect only has vitalism justified itself—namely, as a protest against the physico-chemical theory of life; but it would evidently be a retrograde step to return to the old vitalism.

THE FUNDAMENTAL WORKING HYPOTHESIS OF BIOLOGY.

Many men of science have assumed that the only real explanations of biological phenomena must be mechanistic ones, and that

to give up the attempt at physical and chemical explanation is to give up all attempts at explanation. The basis of this conclusion is the assumption that ultimate reality is physico-chemical reality: that the fundamental working hypotheses which have so brilliantly justified their use in the department of experience dealt with by physics and chemistry correspond accurately with ultimate reality. This assumption is, however, devoid of justification. The philosophical investigation of the last two centuries has very clearly shown that experience as a whole cannot be explained if it be assumed that matter and energy exist in reality just as they are provisionally assumed to exist in the sciences of physics and chemistry. Hence the fundamental conceptions of physics and chemistry have no higher status than that of other provisional working hypotheses, already known not to be capable of universal extension. It follows that there is no warrant for assuming that in biology the working hypotheses of physics and chemistry are the only possible ones. Biology is perfectly at liberty to make use of such working hypotheses as enable biological phenomena to be made as far as possible intelligible. It is not a general system of metaphysics that biology or any other branch of natural science directly aims at; and even if it were, nothing would be gained by attempting to square the facts of biology with a materialistic philosophical system long known to be impossible. For a full justification of this conclusion I should like to refer to Volume I. of my brother's recently published Gifford Lectures.*

I have been compelled, in defence of biology itself, to diverge for a moment from purely biological to general philosophical considerations, and I should like to take this opportunity of entering my very strong protest, as a man of science, against the practice on the part of many men of science of wholly ignoring the results of general philosophical investigation, and proceeding as if these investigations had never been made, or had never led to any results. Men of science are the first to point out the failings of so-called "practical" men, who for want of scientific knowledge are constantly attempting the impossible, or failing to take the means of doing what is obviously possible. In ignoring the

* *The Pathway to Reality*, by R. B. Haldane, 1903.

results reached by the great philosophical thinkers, men of science are just as much to blame as is the manufacturer who ignores physics and chemistry ; and a scientific education which ignores philosophy has precisely the same defects as a technical education which ignores science.

The question we have now to ask is, What fundamental working hypothesis best suits the practical needs of physiology and biology in general ? In considering this question we must, if necessary, boldly brush aside the common preconceptions derived, as has just been pointed out, from obsolete metaphysics.

Biology deals with living organisms, and I have already endeavoured to show that all attempts to get beyond living organisms—to analyse the phenomena of life into terms of mere physical and chemical change—have resulted in a failure that leaves not the remotest hope of success. We must therefore go back to the facts of observation, and settle clearly what they lead us to believe that a living organism is.

In view of these facts, a living organism must, it seems to me, be defined as a being which manifests its existence in the active maintenance and reproduction of specific structure, or in the maintenance and reproduction of activity in specific form. Its characteristic details of structure, qualitative and quantitative, are by this definition set down as the active expression of its existence, or as the form of activity in which its existence is expressed. Only by such a definition can we describe the characteristic autonomy of a living organism.

In the world as it is assumed to be in the sciences of physics and chemistry, matter and energy are regarded as two distinct forms of existence, the association together of which in any particular form or degree is accidental. The above definition of a living organism implies that in life the separation in thought of matter from energy must be regarded as unreal—that organic structure is identical with specific activity, and that whether we speak of the structure, or the physiological activity of an organism, we mean practically the same thing, since structure is only the specific form in which an organism actively manifests its being. The definition makes it clear that structure and activity in the

physical sense are not the same as structure and activity in the biological sense. The morphological structure may persist, although from the physical standpoint the material of the living body is constantly changing; and physiological activity is not the mere flow of energy in the physical sense through a material structure.

If this definition be admitted the fundamental working hypothesis of biology must be that living organisms, as so defined, exist, just as the fundamental working hypothesis of physics is that matter and energy exist. We must also remember that the two working hypotheses must not be mixed up. Such terms as "living matter," or "molecules of protoplasm," can have no definite meaning. To those who insist that the living body can only be composed of atoms or molecules we must offer the reminder that atoms or molecules only represent a working hypothesis of limited application, and that we do not yet know what may be hidden behind these conceptions. We have now to see how the definition which has just been given of a living organism can be utilised as a fruitful working conception in physiology. Only by its utility can it be tested. There is no other real criterion.

It is evident that when we start from this definition our scientific aim must be to exhibit by observation and experiment each detail of organic structure or activity as a part of the organic whole, in which the nature of any living organism manifests itself. Starting with only the indefinite general conception that the organism is an organism, we have to gradually fill in the details by experimental investigation, and make our conception of it more and more definite. At first we are confronted by a confusing mass of observations of physical structure, chemical composition, movements, chemical changes, etc. These are the sensuous data which we have to investigate with the object of revealing their real interpretation. Our aim is to render them intelligible by sifting out what is accidental and irrelevant, and gradually discovering more and more fully their true interpretation as manifestations of an organic whole. Our ground conception, or

fundamental working hypothesis, is evidently a teleological one ; hence biological explanation can only be teleological explanation.

This ideal differs essentially from the mechanistic ideal, and seems, when we look back at the actual progress of biological investigation, to correspond far better with the direction which this progress has taken. It cannot be said that if we compare, for instance, the physiology of Descartes' physiological treatises, *De Homine* and *De Formatione Fœtus*, with the physiology of the present time, any progress can be traced towards the realisation of the mechanistic ideal which he so clearly put forward in these books. Indeed, the realisation seems infinitely further away now than it probably did then. The mechanistic physiology has further tended to set up an artificial barrier between anatomy and physiology by making structure the basis of explanation of function, and relegating questions relating to the formation of structure to a separate domain concerned with questions so difficult that they afford no hope of fruitful investigation. It is only quite recently that the development of experimental embryology has begun to break down this artificial barrier, the existence of which has been a great hindrance to biological advance.

The mechanistic ideal has also tended to discourage teleological investigation. The mechanistic physiology implies that the teleological regulation of the structure and functions of the body is merely accidental. Consequently investigations of this teleological regulation have been relegated to the background. Much knowledge has been accumulated about the effects of this or that experimental procedure while the directly important question of how function is regulated teleologically under normal conditions has been relatively neglected. To take concrete instances, instead of an account of how secretion of urine, absorption from the intestines, or circulation of blood, is normally regulated as participating in the maintenance of the organism, we are apt to find in current text-books elaborate discussions of the imaginary "mechanisms" of respiration, secretion, absorption and circulation—mechanisms which, if they exist, must act with blind disregard of organic unity, although they usually happen to act conformably to it.

When we look at the history of physiology, not from the standpoint of the mechanistic ideal, but from that of what may be called the biological ideal, which I have endeavoured to formulate, the progress which has been made appears continuous, if often one-sided owing to deflections produced by waves of misleading theory. It has been recognised from the earliest times that apart from any conscious volition an organism displays unmistakeable autonomy in maintaining its normal structure and physiological activities and so asserting its identity as a living organism. In face of injury or disease or disturbance of any kind, it tends to return to the normal. It regulates the breathing and the ingestion of food; its own growth; its temperature; its secretions and excretions, and other bodily functions. This self-assertion or autonomy has, of course, at various times been referred to the presence in the body of "vital spirits," the "soul" acting unconsciously, or "vital force," but as physiology has progressed, so has knowledge of organic autonomy steadily extended and become more precise, apart altogether from animistic, vitalistic, or mechanistic theories. The rise of comparative anatomy and physiology, and the discovery that organisms are related to one another by descent have further shown that the same structure and activity as is manifested in the lives of organisms of one species can be traced also in the lives of organisms of other species. The evidence of progress seems quite inconclusive so long as it is assumed that the question for physiology is: by what mechanisms or what interference of "vital force" is the appearance of teleological regulation in the physical and chemical processes occurring in organisms produced? But if a living organism is taken to be a living organism and nothing else, the question becomes: in what manner do living organisms manifest their being and identity? And to this last question physiological investigation is giving a more and more complete answer with every succeeding year. New details of process and structure are constantly being discovered on the one hand, while, on the other, experiment and observation are constantly showing how in these details organisms are expressing and preserving their own identity.

It is of course impossible to undertake in the course of two lectures any detailed survey of the different departments of physiology; but I propose in my next lecture to indicate in outline the lines of advance along which it seems to me that progress in each department has occurred and further progress may be looked for.

LECTURE II.

In my first lecture I endeavoured to show that while the old vitalistic working hypothesis in physiology was altogether unsatisfactory, the mechanistic hypothesis which, some fifty years ago, replaced it is inconsistent with the observed phenomena, and must therefore also be rejected. I then proceeded to argue that in biology the fundamental working conception, beyond which we cannot get, is that of the living organism. In the present lecture I propose to indicate in very bare outline the lines upon which physiology appears to have advanced and be advancing with the help of this conception.

What I have to say must be confined to the physiology of the higher animals, as to which our knowledge is far more extended and precise than in the case of lower animals. It might be contended that it would be preferable to refer only to the lower and simpler organisms, and not to those in which natural selection has produced great complication of structure and function. I have already pointed out, however, that natural selection is itself an organic process, in which only the characteristic features of life itself are developed; and this being so it is evidently preferable to consider the higher organisms, about which most is known and which are most easily investigated.

ANIMAL METABOLISM.

I will first refer to the general physiology of animal nutrition or metabolism in mammals. Starting from our fundamental conception, we have evidently to consider, in connection with this subject, how the living organism asserts itself as an organism in the main exchanges of material and energy between itself and

the environment. The form in which this problem is stated assumes that it is an organism and not a mechanism that we are investigating, and that we are seeking, not for physico-chemical explanations, but for what we can recognise to be the modes of activity of a living organism, this recognition constituting the only explanation expected.

Our knowledge of animal metabolism, as exemplified in the higher animals, starts from the fact of common observation, that in spite of losses and gains the body maintains its substance and activity at a fairly constant level. Closer investigation has defined more and more fully the sources of loss and gain. It has been discovered that one great source of loss of material is the carbon dioxide in expired air; another the nitrogenous compounds of the urine; another the water given off by evaporation and in the urine; another the inorganic salts of the urine; and that the main loss of energy is in the form of heat and muscular work. Similarly, the main sources of gain of material are the oxygen of the inspired air; the carbon, hydrogen and oxygen of carbohydrate, fatty, and proteid food; the nitrogen of proteid food; the water and salts taken with the food; while the potential energy of proteid, carbohydrate and fat constitutes almost the sole source of gain of energy.

Mere knowledge of the sources of gain and loss would not, however, be physiology, but only physiological chemistry or physiological physics—only part of the sensuous material of physiology. To convert this knowledge into true physiological knowledge further investigation has been needed of the relations between each source of loss and gain and the other organic processes. We might imagine a body so constituted that its losses of material and energy depended simply on the quantity of food material and oxygen supplied to it, just as the production of carbon dioxide, heat, etc., from a furnace depends on the quantity of fuel and oxygen supplied. Actually it was at one time assumed that, practically speaking, the body is so constituted. Such a body would be, not an organism, but a machine. In the actual living body the gains and losses have been found to be closely related to the maintenance and reproduction in both function and

structure of the organism as a whole. Neither intake nor output of material or energy occurs independently of physiological requirements.

Let us consider first the output of carbon dioxide in respiration, and endeavour to follow out the conditions on which it depends. In the first place this output is dependent on the respiratory movements. These are, however, so controlled that the lung-ventilation corresponds with extraordinary exactitude to the production of carbon dioxide. The result of this is that the blood passing through the lungs is freed from carbon dioxide to practically the same extent whether the production of CO_2 in the body is increased or diminished. The partial pressure of carbon dioxide in the blood and tissues is thus kept constant, and the harmful consequences known to result from an abnormal partial pressure prevented. We have every reason to believe that in bringing about this result the circulation is controlled similarly to the respiration, although experimental evidence on this point is not yet complete.

The production of CO_2 in the body has been found to depend on the constant vital activity of every part of it—muscles, glands, nervous system, alimentary canal, connective and supporting tissues, etc. The old idea that CO_2 production is mainly a simple oxidation process occurring in the fluids of the body, and dependent merely on the supply of oxygen and oxidisable food material in these fluids, has been shown to be devoid of foundation. The production of CO_2 is intimately dependent on the life of all the tissues. In other words, it depends on all the conditions, structural and functional, on which the life of the organism as a whole depends; and to discover any true physico-chemical explanation of its production is the same hopeless task as to discover a physico-chemical explanation of life itself. We may discover chemical precursors of CO_2 , or chemical conditions on which its *immediate* production depends, but it is quite certain that any such discoveries can only bring out still more sharply the dependence of CO_2 production on life. The main problems connected with CO_2 production in the living body are thus physiological and not merely chemical problems. Further research can

and will reveal in greater detail how CO_2 production and its variations are related to the maintenance of organic structure and function; and the only explanations we need look for are, accordingly, teleological explanations, becoming more and more precise as experimental research advances. We find by observation that the normal production of CO_2 in animals is intimately connected with the other manifestations of animal life. Just as one part of the body is related to the others, so is CO_2 production associated with the various structures and functions of the living body; and there is a normal average measure of CO_2 production just as there is a normal size for the liver or kidneys. We also find that within wide limits CO_2 production is not increased or diminished in proportion to the abundance or scarcity of food or of oxygen; and this fact we can explain, since CO_2 production, which is associated with bodily activity of various kinds and heat-production, depends on physiological requirements, and these do not vary in proportion to abundance or scarcity of food or oxygen. On the other hand, the CO_2 production rises, particularly in small animals, with fall in the surrounding temperature, and not conversely, as might have been expected, the explanation being that increased heat-production, and therefore CO_2 production, is required to keep up the body temperature.

We may next consider the output of nitrogen in the urine. This has been found to be almost exclusively dependent on the breaking down of proteid material, whether derived directly from the food, or from the living tissues. Like the CO_2 output, the output of nitrogenous material, in urea and other forms, is always associated with animal life, but the nitrogenous output varies in a quite different manner from the CO_2 output. The most striking difference is that, provided a certain minimum is not reached, the nitrogenous output varies in more or less direct proportion to the intake of nitrogenous food. There is thus no normal nitrogenous output corresponding to the normal CO_2 output, since the intake of nitrogenous food varies greatly under conditions of ordinary health. This apparently anomalous fact was for long a puzzle, since it seemed to indicate that the organism is wasteful

of nitrogenous food, and throws it away without regard to physiological requirements. The apparent anomaly was, however, cleared up by the work of Rubner, who showed that just in proportion to the consumption of nitrogenous material other material (carbohydrate and fat) is saved, proteid, when it is supplied in abundance, being used up in place of carbohydrate and fat, the one substance being substituted for the other in exact proportion to its energy-value. The discovery of this very beautiful law of substitution at once furnished a clear physiological explanation of many otherwise obscure facts connected with animal metabolism. It is now very evident that under normal conditions the total metabolism of the body, measured in terms of the energy-liberation corresponding to it, is approximately constant, but may be made up in different ways, carbohydrate, proteid, and fat being substituted for one another according to circumstances. If abundance of all be provided, proteid is preferred, and if only carbohydrate and fat are available in abundance, carbohydrate is preferred; fat, which is far the most convenient form in which energy can be stored in the body, being thus always saved wherever possible. So far from there being waste of material in the body there is therefore strict economy, and so exactly is this balance of expenditure of material in terms of energy-value carried out under normal conditions that a living organism might be used as a differential calorimeter for different food materials. By a strange confusion of thought this very fact has been adduced in support of the mechanistic theory of life! When we consider how easily the metabolism is greatly increased or diminished by variations in muscular activity it seems probable that future investigation will reveal in the phenomena of "fatigue," and the tendency to muscular activity seen, for instance, in play, a delicate means of adjustment of the normal energy output.

The output of water has been less fully investigated than that of other substances, but appears to be related closely to physiological acquirements. The proportion of water ordinarily present in the urine would seem to be related to physiological economy in the work of the kidneys, since a very concentrated urine would

imply more work in secretion. The water secreted by the respiratory passages, and thence carried off by evaporation, is evidently necessary for the efficient working of the ciliated epithelium lining the mucous membrane. The secretion of water as sweat from the skin is related to the regulation of the body temperature, and of course varies with the production of heat in the body and with the surrounding temperature, becoming very great when the latter is high.

The output of inorganic salts by the urine is very variable, in marked contrast to the very constant proportions of many inorganic salts in the blood and various tissues. As inorganic salts, although essential to life, are not used up in the body, and hence do not come into the category of waste products, we may regard the salts of the urine as representing in the main a surplus not required, and the presence of which within the body would be actually harmful. This surplus arises in part from salts present in the food, and in part from the constant liberation of sulphuric and phosphoric acids within the body. The only inorganic salt actually added to the food by men and some animals is sodium chloride. As has been pointed out by Bunge, this is probably explained by the fact that though sufficient sodium chloride is naturally present in ordinary food materials, the chlorine, and possibly also the sodium, enter into other combinations in the body, and these combinations are eliminated as foreign and surplus substances. Thus the excess of potash salts in vegetable foods leads indirectly to a loss of sodium chloride, which produces a scarcity of this substance, and a consequent craving for sodium chloride.

A study of the elimination of inorganic salts under different conditions certainly confirms the interpretation just given of the physiology of their output from the body. Thus, when food deprived of its salts is given, the elimination of sodium chloride and other salts falls to an extremely low minimum, although the percentage of salts in the blood and other tissues remains nearly normal. In ordinary starvation, on the other hand, salts are eliminated in proportion to those present in the tissues which break down to supply the bodily metabolism. Hence, for instance,

potash salts from the muscular substance, and phosphate of lime from the bones, are present in abundance in the urine, while sodium chloride is very scarce, since the blood, which is the only tissue containing much sodium chloride, is very slowly used up in starvation.

Coming now to the intake of material, I may refer first to the intake of oxygen. This, like the output of CO_2 , is determined according to the expenditure of energy, and therefore shows the same average constancy and temporary fluctuations, owing to muscular work, etc.

The intake of organic food-material is evidently controlled in accordance with the requirements for maintaining normal bodily activity, although detailed study of this control is still lacking. In the case of adult men the average energy-value of the food has been found to be about 3,500 calories, made up of varying proportions of proteid, carbohydrate, and fat, a minimum of about 50 grammes of proteid (200 calories) being, however, always present. Apart from this necessary minimum it seems to matter little whether fat, carbohydrate, or proteid is used to make up the necessary amount. The amount taken varies, of course, from day to day. When there is an excess this is nearly all stored up as fat, and to a much less extent as carbohydrate and proteid, the reserve of stored material being always large under normal conditions. When there is a deficiency the stored material is drawn upon; and even after prolonged starvation the metabolism during rest remains about the same if measured in energy-value, although the capacity for muscular work is diminished. The size of the body does not vary in proportion to the abundance or scarcity of food-material. It is the organism which determines its own intake of food-material, not the varying abundance of food which determines the size and composition of the organism.

The intake of water, like the intake of food, follows the body's requirements; and just as there is a storage of food-material, as fat, etc., so there is a storage of water, chiefly in the muscles. This store of water is drawn upon during scarcity or excessive sweating, and afterwards replenished. If from any cause, however, a further excess of water is drunk, this is got rid of in the

urine, just as the inorganic salts are. The intake of these latter need, perhaps, hardly be referred to further.

From the foregoing survey of general metabolism as observed in higher animals it seems evident that the phenomena connected with it are only intelligible in the light of the assumption that the nature of an organism is to maintain its fundamental structure, composition, and activities. Its activities do not run down or flare up under the varying influence of environment, like those of a machine; nor does its structure wear away piece-meal. The organism itself exerts an active deciding influence in the give and take between itself and its environment, and unless this fact is taken into account it is impossible to place the physiology of animal metabolism on a sound scientific basis. The crude physical and chemical theories of animal metabolism and tissue growth which became current before the phenomena had been at all adequately investigated have indeed been shattered to pieces by the more exact researches of the last fifty years; and from no department of physiology can stronger evidence be adduced of the characteristic active autonomy of the living organism.

SECRETION AND ABSORPTION.

The physiology of secretion and absorption naturally fall to be considered next; and may conveniently be taken together, since in each case the central phenomenon is a transference of material from one side to the other of a layer of epithelial cells. Both secretion and absorption were for long very generally regarded as essentially processes of mechanical filtration from or to the blood, the nature of the filtrate depending on the sizes and shapes of the pores or fine tubules through which the filtration was supposed to occur, and the process being aided by diffusion. The closer experimental investigation of the last fifty years has, however, rendered this view untenable. As is well known, it has been found that secretion may occur although the pressure in the secreting ducts is higher than in the blood. In other cases also the concentration or partial pressure of the substances secreted is far higher in the secretion than in the blood. Such substances

must be either formed in the gland cells or actively selected by them from the blood. Instances of this kind are afforded by the secretion of urine, in which case the concentration of urea, sulphates, phosphates, urates, etc., may be enormously greater in the urine than in the blood, these substances being selected from the blood, and not formed in the secreting epithelium. Another very simple instance is afforded by the gas in the swimming bladder of fishes. The partial pressure of oxygen in sea water is only about a fifth of an atmosphere, whereas that of the gas secreted into the swimming bladder may amount, in very deep water, to as much as 100 atmospheres. The processes of secretion and absorption have also been found to be accompanied by absorption of oxygen and formation of carbon dioxide, and to be easily affected by drugs and poisons. Lastly, morphological changes of various kinds in the secreting gland cells have been observed to accompany secretion and absorption.

There can thus be no doubt that secretion and absorption are processes which are intimately and directly dependent on the life of the secreting or absorbing epithelial cells. The transference of material which takes place must be regarded as a part of the metabolic activity of these cells. This metabolic activity is evidently continuous, since the cells are extremely sensitive to any interruption of the blood-supply, and are known to be at any rate always absorbing oxygen and producing CO_2 ; but the actual secretion may be intermittent. We can also be certain that their metabolic activity is a very many-sided one, connected in endless ways with the metabolic activity of other cells in the body. Thus the removal or destruction of a gland may have the most complex and far-reaching influence on the rest of the body—an influence which has in various instances been shown not to be due to mere absence of the secretion. Examples of this are furnished by the effects of excision of the pancreas, liver, or kidneys. The mere blocking off or diversion of the secretion from any of these organs has by no means the same effects. In the case of the liver our knowledge of its secretory activity is already overshadowed by what is known of the other metabolism; and there can be no doubt that as investigation advances

great additions to knowledge will be made through the study of the many-sided metabolism of the cells concerned in secretion and other functions.

This metabolism can only be studied fruitfully when it is regarded as playing its part in the metabolism of the body as a whole. It is very evident that in the highly differentiated animal tissues the special physiology of any part of the body is, practically speaking, the physiology of the whole body. The special modifications of form, structure, and metabolic activities in each part are determined by its physiological relations to other parts. Hence, if each part or organ is investigated separately, and without reference to the conception of the organism as a whole, no satisfactory progress is possible: we are simply confronted with a confused collection of unintelligible observations. If the body is regarded as simply a complicated mechanism, it follows that in order to understand it we must study the structure and properties of each part separately, deducing their mode of interaction from the knowledge thus gained. The mechanistic theory of life has unfortunately led to a general adoption of this latter method, with the result that progress has been slow. Much effort has been spent in vain attempts to establish mechanical theories of secretion and absorption, and the negative knowledge which has resulted does not by itself carry us very far. Merely to have learned that absorption and secretion are not filtration or diffusion processes is doubtless important, but we require to understand the normal physiology of the organs concerned.

Although our knowledge of the physiology of secretory and absorbing organs is still very fragmentary, owing partly to the cause just mentioned, much has nevertheless been ascertained from a study of their behaviour under approximately normal conditions, purposely varied experimentally. We know, for instance, that the kidneys react most delicately by increased secretion to any excess in the normal proportion of various substances circulating in the blood; and that secretion by the digestive glands is also regulated, partly through the nervous system, and partly through substances carried in the blood, in accordance with physiological requirements.

Very little is yet definitely known as to the metabolic activity of secretory and absorbent organs apart from actual secretion and absorption; and such knowledge as we possess refers chiefly to the liver, which has been shown to possess the power of arresting and converting various substances—sugar into glycogen, ammonia into urea, hæmoglobin into bile-pigments, etc.

Looking at the physiology of secretion and absorption as a whole we find that these processes are due to the activity of living cells with highly specialised metabolic activities, this specialisation being, so far as our knowledge goes, only intelligible teleologically, as necessary for the maintenance of the rest of the body.

THE BLOOD AND CIRCULATION.

Let us next consider the physiology of the blood and circulation. Apart from the physiology of the heart itself the circulation of blood is intelligible as a purely mechanical process. The action of the blood as a carrier of oxygen, CO_2 , and other substances is, further, perfectly explicable on physical and chemical grounds. It is natural, therefore, that the analogy of the circulation should have been made a main basis of the attempts to show that the whole body is nothing but a complex mechanism. In the famous mechanistic physiology (*De Homine*) of Descartes the circulation was regarded as the motive power for the muscles, nervous system, glands, etc. He even supposed (*De Formatione Fætus*) that the blood-pressure moulds the tissues of the body during foetal life, and that the heart's action itself is due to a mechanical process.

Besides the circulation there are many other mechanical processes connected with the living body. As instances may be mentioned the processes of mastication and swallowing, the ventilation of the lungs with air, the production of voice, the focussing of light in the eye, the conduction of sound waves in the ear, and the action of the various groups of muscles on the bones and joints throughout the body. There are also chemical processes, such as that of digestion, or the taking up and giving off of oxygen and CO_2 by the blood. Many new physical and

chemical processes, both intra-cellular and extra-cellular, are certain to be discovered as investigation advances.

Now let us ask, in the first place, in what sense the organs of circulation, and the other parts of the body concerned with these mechanical or chemical processes, are mechanisms. They are all parts of the living body, have grown and developed with it, and participate in its constant metabolism. There is, for instance, no tissue which, in spite of constant loss and gain, maintains its volume and composition with more striking constancy than the blood. Neither starvation nor ingestion of food and drink materially affect it; liquid injected into it is got rid of with remarkable rapidity; and any loss of blood by bleeding is soon replaced. Yet we know that it is through the blood-stream that all the exchange of material between different parts of the body is brought about. We also know that the blood corpuscles are constantly breaking down and being replaced by new ones, formed in the bone-marrow. This vital metabolism of the circulatory system is doubtless due chiefly to the activity of its lining endothelium, which most certainly does not play the mere mechanical part which has often been attributed to it. The other so-called "mechanisms" can likewise be shown to have all the characteristics of the living body, inasmuch as they actively maintain their structure, just as the organism as a whole does so. There is thus no warrant for calling them mechanisms, and thus ignoring what is one of their essential characteristics.

But there is another fact of equal importance with regard to the mechanical processes in the body—namely, that they are entirely subservient to physiological activity, and can only be understood as forming a part of it. As we have already seen, it was formerly supposed that the circulation of the blood determines various forms of physiological activity, such as secretion, the action of the central nervous system, &c. This was putting the cart before the horse—a process characteristic of the mechanistic theory. In reality the circulation has been found to be only subservient to physiological processes. By means of the vaso-motor nervous system the blood-flow through various organs, such as glands or muscles, is increased or diminished according

to the degree of activity of these organs and consequent need for blood. The altered blood-flow is the result, not the cause, of the variations in activity, since an increased blood-flow does not by itself cause a corresponding increase in activity. Similarly, the variations in the heart's action, the rate of ventilation of the lungs, or of digestive changes, are not determining causes of physiological activity, but subservient to it; and the same is evidently true of the various other mechanical and chemical processes throughout the body.

To sum up, neither the circulatory system nor any other structure in the living body can properly be described as a mechanism; and the mechanical and chemical processes which undoubtedly take place in connection with these parts in the living body are only intelligible as subservient to organic activity.

THE NERVOUS SYSTEM.

I come now to the nervous system. In the treatment of this subject it will be necessary to keep within the bounds of physiology as distinguished from psychology. Men or animals regarded as conscious individuals, the subjects of knowledge and volition, lie outside of the scope of physiology, just as the phenomena of life lie outside the scope of physics and chemistry. Nevertheless it is possible in observing our own sensations to treat them as mere states of the body, and abstract from their psychological aspects. In this way self-observation is legitimately employed in connection with the physiology of the senses and central nervous system generally; and the subjective phenomena observed under this limitation fall within the limits of physiology and not of psychology.

Like the circulatory system, the nervous system, as regards its development and nutrition, is the seat of the same characteristic metabolic processes as the other parts of the body. It therefore cannot be regarded as a mechanical structure. But the processes occurring in it resemble in many respects mechanical processes, and have been commonly regarded as such. We have, therefore, to inquire in what sense this mechanistic interpretation is warranted.

On the mechanistic hypothesis this system is a complicated arrangement of conducting channels—the nerve-fibres, connected at their peripheral ends with all parts of the body, and at their central ends with groups of nerve-cells, acting as centres for the transfer of afferent impulses to efferent nerve-fibres, or to fibres passing to other centres. Both the transmission of impulses and their transfer in the nerve centres are assumed to be mechanical processes dependent upon the physical structure of the nerve-fibres and nerve-centres, any energy required being supplied at the expense of concurrent chemical changes. Simple reflex action is taken as the type of these processes, the more complex nervous responses being regarded as merely very complicated reflex action.

As to the exact nature of the process taking place in the transmission of nerve-impulses we have no very certain knowledge. Nerve-fibrils are undoubtedly living structures; but there is no clear evidence that the characteristic metabolic changes which accompany vital activity in other tissues are associated with the conduction of nerve impulses; and in the absence of such evidence it seems quite possible, though not probable, that the passage of a nerve impulse may be, like the flow of blood through a blood-vessel, in itself a purely mechanical process.

The further mechanistic assumption, that the nature of the response of a nerve-centre depends upon its physical structure, must be carefully considered. If we examine a reflex, such as that of assuming a normal position or removing an irritant, it soon appears that the process is by no means the blind mechanical response which it may at first sight be taken to be. For the actual muscular response varies according to the position from which the limbs are moved or to which they may require to be moved. Indeed, the physical response varies endlessly according to circumstances. It is the end attained, and not the physical response, which is simple and definite. A mechanism which attains ends in this way is inconceivable.

The response is determined, not merely by sensory impressions from any spot stimulated, but also by impressions from many other parts of the body. This is a general characteristic of the activity of the central nervous system, and leads to the conclusion

that in reality the afferent and efferent nerves are in a continuous state of activity, and continuously in active relation with the central nervous system. Further, the strength of the response does not vary in proportion to the strength of the physical stimulus. In other words, the "excitability" varies, depending for one thing most markedly on the state of activity of other afferent nerve-fibres. For instance, light rays of a certain intensity falling on a certain part of the retina may produce either a very marked sensory effect or no sensory effect at all, according to the amount of light falling on other parts of the retina.

But analysis of the phenomena carries us much further. The activity of the nervous system clearly depends not merely on influences from peripheral surfaces, joints, muscles, etc., but also upon influences from visceral organs. These influences are in part transmitted through visceral nerves, but chiefly through the blood. It is a familiar fact that arrest of the circulation, or of the oxygen-supply from the lungs, causes a rapid turmoil in the action of the nervous system, followed by arrest of function, structural changes in the nerve-cells, and death after a short time. A very slight excess or deficiency of carbon dioxide in the blood also produces an alteration of function; and we have every reason to believe that almost any abnormality in the blood—for instance, in the percentage of sodium chloride, potash salts, ammonia, water, or the various special metabolic products of the glands, muscles, reproductive organs, nervous system, etc.—may profoundly modify the working of the nervous system. One or other "reflex" or "instinct" is lighted up or extinguished. A small excess of carbon dioxide in the blood will, for instance, concentrate almost the whole activity of the nervous system on efforts to increase the lung ventilation and rate of blood-circulation, at the same time blotting out the responses to other physical stimuli.

It would thus appear, firstly, that reflex action, even regarded as an isolated phenomenon, has not the characteristics of a mechanical process, and, secondly, that the activities of any part of the nervous system are intimately dependent both quantitatively

and qualitatively on those of other parts of it and of the rest of the body. We can proceed to explain the phenomena if we make the fundamental assumption that the nature of an organism is to maintain and reproduce, in the face of varying environment, its structure and activities as a whole ; but apart from this teleological mode of explanation there is none.

It is characteristic of nervous activity that many of its manifestations occur intermittently and at irregular intervals. It would seem, however, that what appears to superficial observation to be a state of physiological rest is never so in reality. The "resting" tissues can be shown to be the seat of constant metabolic activity, although no external stimulus may be acting on them ; and in the case of the nervous system each part, as already remarked, is constantly in active physiological communication with other parts of the body through the connecting nerve-fibres and the circulation. The more or less explosive outward manifestations of activity are merely temporary fluctuations in this constant activity, which has itself all the fundamental characteristics of organic activity. It follows, therefore, that these same characteristics apply also to the explosive manifestations.

The responses of the nervous system present to a marked extent the superficial appearance of deliberate purpose based on elaborate consideration, although no conscious purpose or knowledge is present. Thus the co-ordinated muscular movements produced by the activity of the respiratory centre are elaborately adapted to the purpose of removing carbon dioxide from the blood and supplying oxygen to it. In a simple undifferentiated organism an increase in the carbon dioxide present in the protoplasm would naturally lead to increased activity in its elimination. The elaborate response to excess of carbon dioxide in a highly differentiated organism is in reality only a development of the same reaction, the efficacy of the response in removing the stimulus being the guiding influence. This is true whether or not natural selection has been a factor in this development. As already shown, natural selection is in itself an aimless process, incapable of bringing about organic evolution, apart from the guiding

influence introduced by the fact that the nature of living organisms is to actively maintain, develop, and reproduce their specific structure and activity; and in order that natural selection should influence the development of a specialised respiratory system we must presuppose that organisms are actively intolerant of excess of carbon dioxide or deficiency of oxygen. The influence of natural selection, whatever it may be, is thus subordinate to the teleological factor, and even in the case of the complex activities of the nervous system the teleological conception is the only one which is ultimately capable of rendering the phenomena intelligible.

It is perhaps scarcely necessary to refer in detail to the physiology of the muscles or the supporting and connecting tissues of the body. On the one hand, the nutrition of these living parts of the organism is determined with reference to the whole, just as in the case of other living parts. On the other hand, their more specialised vital and mechanical activities are under the immediate control of the nervous system, to which reference has already been made.

CONCLUDING REMARKS.

I have now completed a very cursory survey of the data of physiology in their bearing on the question before us, and have endeavoured to illustrate in some detail the necessity for making the fundamental assumption that the living organism is an organism and not a machine.

There is a point which may be urged in objection, and to which I wish to refer briefly. Physiological investigation is based on observation and measurement of changes which can, when taken by themselves, only be stated in physical and chemical terms. We observe and measure the intake, output, and exchange within the body of various chemical materials and forms of energy; also various changes in the mass and form of different parts of the body. These observations, it may be pointed out, are physical and chemical observations, expressed in terms of the fundamental working hypotheses of physics and chemistry.

Hence, it is argued, physiology can be nothing else but the application of physics and chemistry to the phenomena of life, however imperfect and unsatisfactory this application may be. If we start from physical and chemical phenomena, we can never relate them to anything else but other physical and chemical phenomena, since any such relation would be totally unintelligible.

In answer to this objection, I would point out that in biology the phenomena which are or ought to be observed from the very beginning are not physical and chemical phenomena as self-existent events, but these phenomena as expressions of the activity of living organisms. It is the living organism, and not the physical phenomenon, which is the reality for biology. In precisely the same way the phenomena of extension, form, movement, colour, etc., are treated in the physical sciences as the expressions of matter and energy, these latter representing the conceptions by means of which the sensuous data are interpreted.

For biology the world is not a world of matter and energy, but of living organisms in an environment organically related to them. The world of actual experience can only be partially brought under biological conceptions or those of any other science. The fundamental conceptions of the sciences are only working hypotheses, adequate in each case to only certain aspects of experience. Hence it is that in our ordinary experience organisms, and particularly their environment, may, and indeed must, be regarded from the merely physical and chemical standpoint, as well as from the biological standpoint. Nevertheless the ultimate ideal of biology must necessarily be to extend biological conceptions to what we at present regard as inorganic phenomena; and perhaps recent discoveries as to the ultimate nature of atoms are pointing towards the possibility of this ideal being realised, and of the physical sciences thus joining hands with biology.

I should like, in conclusion, to summarise the main contentions brought before you in these lectures. I have endeavoured to show that in physiology we must start from the teleological conception of the living organism, since living organisms cannot be explained as either pure mechanisms, or mechanisms guided by some extraneous influence, such as the so-called "vital force,"

and there is no sound philosophical basis for the contention that in physiology physico-chemical explanation is the only real explanation : that all physiological explanation must accordingly be, in the long run, teleological explanation ; and that we are thus furnished with an effective working hypothesis, with the help of which physiology can advance steadily and progressively.

Those who are inclined to disagree with these conclusions will at any rate agree with me in this—that the final test of any scientific hypothesis is its utility. I am far from maintaining that the mechanistic theory of life has not, for want of a better, been of great service to physiology in the past ; but I think it has done its work and lost its usefulness, and that the time has now come to replace it.

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SECRETION BY THE RENAL TUBULES IN THE FROG.

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INTRODUCTION.

IN spite of the large amount of experimental work which has been performed in order to elucidate the function of the renal tubules, it cannot be said that any experiment has yet shown, beyond all question, either that they can secrete or that they can absorb, although it is clear that they must do one or both of these. Nussbaum's experiments still seem to offer the only crucial method of testing the truth of the Bowman-Heidenhain view.

Halsey has fully confirmed and extended Nussbaum's results. He found in ligatured frogs that urea and indigo-carmin were secreted, whereas dextrose, egg-albumin, peptone, and carmine were not. He confirmed the statements of Mosberg and Marcuse that under the influence of phloridzin dextrose is secreted, and showed that the same was true when diuretin was injected simultaneously with dextrose. He found sodium chloride, sodium phosphate, and sodium sulphate regularly present in the urine after they had been injected. These experiments do not prove conclusively that the tubules can secrete, for a

microscopical examination of the kidneys showed in every case, without exception, a greater or less number of glomeruli still in circulation.

Owing to the importance of the subject it seemed necessary to perform further experiments of the same kind, with the object of deciding whether or not results similar to those of Nussbaum and Halsey could be obtained when all the glomeruli were out of circulation.

One of us (A.P.B.) has previously confirmed Nussbaum's statement that complete ligature of the arteries supplying the kidneys cut all the glomeruli permanently out of the circulation. Nussbaum's statement that injections of urea into a fully ligatured frog cause a secretion of urine was not confirmed, at any rate when the injections were begun as late as two days after the ligature. It was also found that cutting off the arterial blood supply of the kidneys caused the epithelium of the tubules to degenerate rapidly, presumably owing to a lack of a sufficient supply of oxygen. The failure of urea to cause a secretion of urine might have been due either to the absence of glomeruli in circulation, or to the degeneration of the epithelium.

The present experiments deal first with the injection of urea beginning directly after the ligature; the result of this was negative. Secondly, they deal with the questions whether by keeping ligatured frogs in oxygen the degeneration of the epithelium can be prevented,¹ and a secretion of urine then obtained; both of these points are answered in the affirmative.

METHOD OF EXPERIMENT.

The method of operation was essentially the same as that used previously. The frogs were always anæsthetised with the A.C.E. mixture throughout the operation. Before the operation

¹ Miss Cullis, *Journ of Physiol.* (1906), xxxiv., p. 250, states that Brodie suggested the use of oxygen in November, 1905, and that we have carried his suggestion into effect. We wish to point out that our experiments were begun early in October, 1905. Further, in Starling's *Elements of Human Physiology*, 5th edition (1902), p. 451, at the end of the account of Beddard's results this statement is made:—"It is evident that some means must be devised of repeating these experiments while ensuring an adequate supply of oxygen to the tubular epithelium."

was begun, the bladder was emptied with a catheter, and the bladder was seen to be empty during the operation. The kidneys were reached through a ventral incision. All the branches given off from the aorta between its bifurcation and the origin of the coeliaco-mesenteric artery were divided by means of the cautery; the coeliaco-mesenteric artery was exposed in its course from the aorta to the spleen, and all vessels given off from it tailwards were divided. The whole operation lasted about half an hour. Male specimens of *Rana temporaria* alone were used, and in all cases the testes and fat bodies were removed.

At the end of the operation, the anus was tied and a solution of urea, etc., was injected. All injections were made either into the dorsal lymph sac, or under the skin of the thigh. The frogs were placed with water under a large bell-jar filled either with air or with nearly pure oxygen under atmospheric pressure.

The experiments were carried out during the winter months. The frogs were not fed, and were kept in a very cool place. Throughout the course of an experiment the anus remained ligatured, except when the bladder was being catheterised. At the end of the experiment the frog was pithed and the vascular system was well washed out from the aorta with normal salt solution, and then thoroughly injected with a saturated solution of soluble Prussian Blue. Serial sections of each pair of kidneys were cut out of paraffin.

RESULTS.

Three frogs, after the operation, were injected with urea and kept in air (Experiments 1-3). Each received one or two subsequent injections of urea; they secreted no urine, and at the end of three days were killed. In their kidneys no glomeruli were injected, and the epithelium of the tubules had undergone degeneration. It would be surprising if epithelium, undergoing such a profound change within three days, were capable of secreting at any period after the ligature. If, however, as in Halsey's experiments, the ligature was incomplete, urine could be produced not only by the glomeruli in circulation, but also by some of the tubules. For it has been shown previously that the

epithelial degeneration does not take place in those portions of a kidney still supplied with arterial blood.

We conclude, therefore, that the positive results obtained by Nussbaum and Halsey were possible only because their ligature was never complete. Whilst Halsey admits that the ligature in his experiments was incomplete, he adds that the number of glomeruli in circulation was too small to be of physiological importance. Nussbaum did not inject the vascular system of the frogs at the end of his experiments, and there is, consequently, no evidence that his ligature was ever complete when he obtained a secretion of urine.

In all the frogs, twelve in number, which were kept in oxygen after the operation, and in which the ligature was found to be complete, the epithelium of the tubules was microscopically normal. It seems clear, therefore, that the degeneration observed in the kidneys of the frogs kept in air is due to a diminished supply of oxygen to the renal epithelium.

In six of these twelve frogs fluid was found in the bladder after injections of urea, alone or in combination with dextrose, phloridzin or Na_2HPO_4 (Experiments 4-9). In the other six no fluid, or at most a few drops, was found in the bladder. (Experiments 10-15.) In one of these normal salt solution alone had been injected, in another urea and Na_2HPO_4 , and in four urea and phloridzin.

Before concluding that the six positive results were due to a secretion of urine by the renal tubules, it is necessary to show that the fluid could have reached the bladder by no other route than the ureters. The other possibilities are the anus, the rectum, and secretion by the walls of the bladder itself. The first is excluded by the continuous ligature of the anus, and the other two would seem to be excluded by our six negative results. But in order to exclude definitely the possibility of secretion by the walls of the bladder, two other experiments were performed. (Experiments 16-17.) In these two frogs both ureters, the anus and the rectum above the bladder were ligatured and injections of urea, or urea in combination with Na_2HPO_4 or phloridzin, were given. In neither case was any fluid found in the bladder. The

possibility that fluid in the bladder could have been derived from the rectum is excluded by the following considerations:—In no case, *post-mortem*, was the rectum found distended with fluid; the drop or two of fluid in the rectum is brown and contains brown flakes, whilst that in the bladder is clear and almost colourless. Further, in two of the positive results (Experiments 8 and 9) the rectum had been tied above the bladder at the operation. This was done because it was found that injections of Na_2HPO_4 and phloridzin sometimes set up slight diarrhoea, so that in passing the catheter into the bladder the eye might become fouled with a few brown flakes which might interfere with determinations of the acidity of the urine.

We conclude, therefore, that the fluid obtained from the bladder was urine secreted by the renal tubules, and that secretion of urine can be obtained in fully ligatured frogs, provided they have been kept in oxygen.

No. of Experiment.	Material injected.			Quantity of urine in twenty-four hours.	Acidity.	Urine contained.
4	Urea	$\left\{ \begin{array}{l} a \text{ 0.5 c.c.} \\ b \text{ 1.0 c.c.} \end{array} \right\}$...	Urea and salts
5	"	1.0 c.c.	...	" "
6	"	0.5 c.c.	1.9	" "
7	Urea and dextrose			0.5 c.c.	...	Dextrose, urea and salts
8	"	phloridzin		0.5 c.c.	2.0	" "
9	"	Na_2HPO_4		$\left\{ \begin{array}{l} a \text{ 0.5 c.c.} \\ b \text{ 0.25 c.c.} \end{array} \right\}$	$\left\{ \begin{array}{l} a \text{ 2.4} \\ b \text{ 2.5} \end{array} \right\}$	Urea and salts

The table shows the quantity and the composition of the urine secreted by the six fully ligatured frogs. None of them secreted during the first day after ligature, and this is not surprising considering the severity of the operation. Incompletely ligatured frogs, however, may secrete urine within twenty-four hours of the operation. (Experiments 21 and 22.) The greatest quantity of urine secreted in a day by a fully ligatured frog was 1 c.c. Observations on normal frogs of the same size kept under the same conditions showed that they might produce as little as 0.25 c.c., and not more than 1 c.c. in a day. When, however, the normal frogs had received injections of urea, etc., the quantity of urine was four or more times greater than that produced by ligatured frogs after the same injections. This difference may be amply

accounted for by the absence of glomeruli in the one case. For whatever difference of opinion there may be as to how the glomerulus works, a consideration of its structure hardly leaves room for doubt that it is a mechanism which can pass out large quantities of water.

The urine secreted by the ligatured frogs contained, in all cases, urea. This was recognised by the production of urea nitrate crystals. It contained also chlorides and sulphates, which were demonstrated by the ordinary qualitative tests. No quantitative estimations of these constituents could be made in the small quantities of urine available. Urates and phosphates never could be demonstrated even after the injection of Na_2HPO_4 , and the same was true of similar quantities of urine obtained from normal frogs. The urine, like that of normal frogs, gave a reddish colour with a saturated solution of picric acid and 10 per cent. NaOH similar to that given by kreatinin in solution, but no attempt was made to demonstrate conclusively the presence of kreatinin.

Five fully ligatured frogs had received injections of phloridzin and urea. In one only (Experiment 8) was a secretion of urine obtained. This urine gave a red colour with a solution of ferric chloride similar to that given by the original phloridzin solution, and reduced Fehling's solution readily. No attempt could be made to identify the reducing substance present, but it was considered to be dextrose for the following reasons:—It is recognised that injections of phloridzin produce glycosuria, and it was found that the urine of neither ligatured nor unligatured frogs ever contained a substance which reduced Fehling's solution unless phloridzin or dextrose had been injected.

This experiment shows that phloridzin can produce glycosuria by acting on the renal tubules. It confirms the conclusions reached by Mosberg, Marcuse, and Halsey as the result of similar experiments. It cannot, however, be held that any of these previous experiments have proved the point. For Halsey admits the presence of glomeruli in circulation. And Mosberg in only one of his experiments injected carmine in order to see that his ligature had been complete, and in that experiment he found glomeruli in circulation. He quotes two experiments with

phloridzin performed by Marcuse in which also no injection of the vascular system was made.

Although it has been shown that phloridzin can produce glycosuria by an action on the renal tubules, it does not follow that in normal animals there is no action also upon the glomeruli. The fact that it was found difficult in fully ligatured frogs to obtain a secretion of urine after phloridzin, although secretion occurred readily in unligatured ones (Experiment 20), is open to two interpretations. It would be possible to believe that phloridzin acts upon the glomeruli as well as on the tubules. It might equally well be that the tubule epithelium of ligatured frogs kept in oxygen, although normal in appearance, is not sufficiently normal in function to react to phloridzin or that the epithelium is not in condition to withstand the deleterious action of phloridzin. These experiments seem to favour the latter supposition. For it was found much more easy to obtain a secretion of urine when urea had been injected alone than when the same dose of urea had phloridzin added to it.

Dextrose together with urea was injected into two frogs. In one the ligature was slightly incomplete (Experiment 22), but in the other it was complete (Experiment 7). Both secreted urine which reduced Fehling's solution readily. The injection of 0.1 gram dextrose into a frog of this size leads to hyperglycaemia. For it was found that when this dose had been injected into a normal frog the urine of the next twenty-four hours contained 0.06 gram and for another day reduced Fehling's solution slightly (Experiment 19). We conclude that in a condition of hyperglycaemia the renal tubules can secrete dextrose.

This conclusion is opposed to the results obtained by Nussbaum, Mosberg, and Halsey. It is only in Halsey's experiments that there is any information about the completeness of the ligature. If, as he believes, dextrose is passed out by the glomeruli alone, and in all his experiments glomeruli were in circulation, it is difficult to understand why he never found dextrose in the urine, except when he had given diuretin at the same time. And the same is true of Nussbaum's and Mosberg's experiments. Although in these there is no microscopical examination of the kidneys to

show that glomeruli were in circulation, we infer that such must have been the case, otherwise their frogs kept in air would not have secreted urine at all.

Some observations were made upon the acidity to phenolphthalein of the urine of ligatured and unligatured frogs. A method of estimation suitable to the small quantities of urine available had to be employed; and the following was found to give concordant results. Urine was sucked up to the mark 1 on a Thoma-Zeiss white blood corpuscle haemocytometer. The stem of this instrument below the bulb is divided into tenths up to 1. This volume of urine was blown into a watch-glass and $\cdot 05$ of the same volume of a weak solution of phenolphthalein was added. With the same pipette measured quantities of $\frac{N}{100}$ NaOH were added, the mixture was stirred with a fine glass rod after each addition and held over white paper in a good light. The first tinge of pink in the fluid was taken at the end point. The urine of frogs is almost colourless; consequently the end point of the reaction is not obscured by the colour of the fluid. The acidity of the urine is expressed in vols. of $\frac{N}{100}$ NaOH necessary to make 1 volume of urine just alkaline to phenolphthalein.

The acidity of the urine of normal frogs was found to vary widely. Thus one frog (Experiment 18) passed 0.25 c.c. urine with an acidity of 2.3, whilst in another (Experiment 9) the acidity approximated to that of the blood to phenolphthalein, in that the slightest addition of alkali made the urine alkaline. Between these two extremes intermediate figures were obtained in other cases. The most frequent figures were about and generally less than 1. The acidity was influenced in the usual way by the injection of drugs. Thus in Experiment 18 urea injections reduced the acidity from 0.6 to 0.2, and the injection of Na_2HPO_4 raised it to 1.5.

Four estimations were made of the acidity of the urine of fully ligatured frogs. In Experiment 6 after injections of urea the acidity was 1.9, and in Experiment 8 after injections of phloridzin and urea it was 2.0. In Experiment 9 the urine before the operation was only just acid to phenolphthalein, but after ligature

and the injection of Na_2HPO_4 and urea it had an acidity of 2.4 and 2.5 on successive days.

We conclude from these results that the tubules can secrete a fluid which is more acid to phenolphthalein than the blood or than the urine turned out by the glomeruli during a glomerular diuresis. Our results confirm those of Dreser. He showed that by injecting acid fuchsin into normal frogs the glomeruli remained uncoloured, and that the fluid and cells of the tubules were red and therefore acid to this indicator. It must be remembered that the uncoloured condition of the glomeruli might be due, when the secretion of urine was small, just as much to the absence of secretion by the glomeruli as to the secretion by them of an alkaline fluid. When acid fuchsin was injected into ligatured frogs the red colour was still seen in the tubules. From this Dreser concluded that the difference in reaction between blood and urine was due to the secretion of acid radicles by the tubules and not to the absorption of bases from a glomerular filtrate. The only source of fallacy in Dreser's experiments is the possibility that his ligature was not complete. He did not inject the vascular system at the end of an experiment, and as he used a dorsal method of ligature similar to that used by Adami it is certain—as has been shown by one of us—that his ligature was incomplete. His control experiments in which he tested his method of ligature by injecting vermilion into the anterior abdominal vein, never showed injected glomeruli. This must mean that his method of injection was unable to show with certainty when glomeruli were in circulation.

Our results, like those of Dreser, are not compatible with the view put forward by Cushny, namely, that the normal difference between the reaction of blood and urine is brought about, not by the addition of HPO_4 , anions to a glomerular filtrate, but solely by the absorption from that filtrate of Na^+ kations in combination with OH or HCO_3 . These experiments on ligatured frogs do not prove that absorption may not play a part, but only that it is not the sole mechanism at work.

It seems at first sight a little surprising, if secretion is a normal function of the renal tubules, that this epithelium after ligature

should not secrete spontaneously, but should need a powerful stimulus in the shape of large quantities of urea. Nussbaum, Adami, and Beddard have all found that frogs kept in air after ligature do not secrete spontaneously; and this is true even when the ligature is moderately incomplete. But in these frogs much of the epithelium has visibly degenerated and probably none of it is strictly normal. The case seems different, however, with frogs kept in oxygen. In Experiment 15, normal salt solution alone was injected in the hope of obtaining a spontaneous secretion. The frog apparently had bled more at the operation than was thought at the time. The result was negative. The attempt to obtain a spontaneous secretion was not persisted in, as our primary object was to obtain positive results if possible. But even in oxygenated frogs the epithelium can hardly be functionally normal, although it appears so microscopically. For in Experiment 14, in which no adverse circumstance such as hæmorrhage was present, injections of urea and Na_2HPO_4 failed to produce any secretion of urine. Nor can it be a matter of indifference to the kidney that it should be cut off from its high pressure blood supply.

The frogs in the other four experiments with negative result had received injections of phloridzin as well as of urea. As in two of these (Experiments 10, 11) not more than the very slight unavoidable hæmorrhage had taken place at the operation and there had been no post-operative oozing of blood, we believe that the main adverse factor at work was damage done by phloridzin to an already depressed epithelium.

CONCLUSIONS.

The experiments which we have carried out seem to prove two facts, namely, (1) that the renal tubules of the frog can secrete; and (2) that they secrete urea, chlorides and sulphates, and dextrose during hyperglycaemia and after injections of phloridzin. It is possible that they secrete kreatinin and, judged by the reaction of the urine, phosphates—in fact most of the normal urinary constituents. This fully confirms the view of the function of the tubules put forward originally by Bowman and then by Heidenhain.

According to the view of Ludwig, elaborated by Starling, the fluid turned out by the glomeruli is a mechanical filtrate and must be isotonic and identical with the blood plasma except for the absence of proteids. This view entails the further supposition that the main function of the tubules is to absorb water, dextrose, bases, etc., and so to concentrate the glomerular filtrate. In order to explain the production, during some diureses, of urine with Δ very much less than that of the blood plasma, Starling has suggested that the tubules may then secrete an extremely hypotonic fluid. We have found, however, that, when the tubules do secrete in response to urea and water, they turn out a urine which contains besides other crystalloids certainly as much urea as that of normal frogs. Although this observation does not disprove the view that the glomerulus is a mechanical filter, it renders filtration extremely unlikely, and, therefore, necessitates a belief that the glomerular epithelium secretes. And again, if both the glomeruli and the tubules can secrete, there is no longer any necessity to believe that the tubules also absorb. But, whilst there certainly is no experiment which proves that the tubules can absorb, there is equally none which shows that they are unable to do so. Absorption by the tubules must be left an open question to be proved or disproved by future experiments. It is clear, however, that no view of the function of the renal tubule can be considered adequate and final which does not explain the function of its different parts corresponding to their variations in structure.

Starting from the observed fact that the tubule can secrete and from the suppositions that the glomerulus also secretes and is a mechanism whose most important function is to pass out any excess of fluid, and remembering that the only known difference between the urines secreted by the glomerulus and tubule, is that one is always and the other never acid to acid fuchsin, we would suggest the following working hypothesis of the secretion of urine:—Both the glomerular and tubule epithelia definitely secrete urine, and in all probability both can secrete much the same urinary constituents in solution. At times when the quantity of fluid to be secreted from the blood is comparatively

small the urine represents for practical purposes the secretion of the tubules, because the epithelium covering the glomeruli is insignificant in extent as compared with that of the tubules. When, however, as during saline diureses, large quantities of water and salts have to be passed out, the mechanism which removes rapidly the bulk of this fluid is the glomeruli; consequently at the height of such a diuresis the urine secreted by the glomeruli very greatly exceeds that being secreted at the same time by the tubules. During saline diuresis the urine approximates more and more to the composition of blood plasma minus proteid, whereby the maximal amount of material is excreted with minimal expenditure of energy by the kidney cells. This power of the glomeruli to get rid of fluid is a true secretion which is generally greatly assisted by increased blood flow through the kidney, but can take place independently of the vascular changes. In other words, the primary factor in such a diuresis is not the vascular change but the state of activity of the glomerular epithelium. If once it is admitted that vascular changes alone cannot set up diuresis by increased glomerular filtration, then it seems necessary to believe with Eckhard that the state of activity of the renal epithelium can be influenced directly by the central nervous system, and that the nerve endings described by Berkeley in the renal epithelium represents the terminations of this nervous supply. Otherwise it seems impossible to explain a diuresis caused by disturbance of the medulla oblongata; for there is no reason to believe that a change in the composition of the blood takes place in such a nervous disorder. It is further probable that all diureses are not solely and entirely of glomerular origin, but that some depend largely upon an increased activity of the tubular epithelium.

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DETAILS OF THE EXPERIMENTS.

SOLUTIONS USED FOR INJECTION.

- a. Urea solution = 10 per cent. urea in normal salt solution.
 - b. Dextrose and urea solution = 5 per cent. dextrose and 10 per cent. urea in water.
 - c. Phloridzin and urea solution = 5 per cent. phloridzin in the urea solution.
 - d. Na_2HPO_4 solution = 5 per cent. Na_2HPO_4 in water.
 - e. Dextrose solution = 10 per cent. dextrose in water.
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Experiment 1.—1905.

- Oct. 31. Usual operation. Emptied bladder. Injected 1 c.c. urea solution. Placed in air.
- Nov. 2. No urine. Injected 2 c.c. urea solution. Tied anus. Air.
- " 3. No urine. Washed out and ligatured the vascular system. Microscopically: no injected glomeruli; epithelium throughout much degenerated.

Experiment 2.

- Nov. 3. Usual operation. Very little hæmorrhage at operation. Emptied bladder. Tied anus. Injected 2 c.c. urea solution. Placed in air.
- " 4. No urine. Tied anus. Injected 2 c.c. urea solution. Air.
- " 5. No urine. Tied anus. Injected 2 c.c. urea solution. Air.
- " 6. 11 a.m. Frog lively. Injected 1 c.c. urea solution. 5 p.m. Pithed frog. *Post-mortem*: Viscera of normal colour and not pale. Two drops of blood-stained urine found in bladder. Washed out and injected the vascular system. Microscopically: no injected glomeruli; epithelium moderately degenerated throughout.

Experiment 3.

- Nov. 10. Usual operation. Some hæmorrhage from one of the renal arteries during the operation. Emptied bladder and tied anus. Injected 1 c.c. urea solution. Placed in air.
- " 11. Injected 1 c.c. urea solution. Air.
- " 12. No urine. Tied anus. Injected 1 c.c. urea solution. Air.
- " 13. No urine. Frog rather feeble. *Post-mortem*: Bladder found empty. All viscera very pale. Much blood in the peritoneal cavity. Washed out and injected the vascular system. Microscopically: no injected glomeruli; epithelium very degenerated throughout.

Experiment 4.

- Nov. 14. Usual operation. Emptied bladder and tied anus. Injected 2 c.c. urea solution. Placed in oxygen.
- " 15. No urine. Tied anus. Injected 2 c.c. urea solution. Oxygen.
- " 16. 0.5 c.c. urine in bladder. Tied anus. Injected 2 c.c. urea solution. Oxygen. Urine contained urea, chlorides, and sulphates.
- " 17. 1.0 c.c. urine, which contained urea, sulphates, and chlorides. Frog fairly lively, but generally œdematous. *Post-mortem*: Viscera not pale. Rectum empty. Washed out and injected vascular system. Microscopically: no injected glomeruli; epithelium normal in appearance.

Experiment 5.

- Nov. 14. Usual operation. Very little hæmorrhage at operation. Emptied bladder and tied anus. Injected 1 c.c. urea solution. Placed in oxygen.
- " 15. Two drops of blood-stained urine in bladder. Tied anus. Injected 2 c.c. urea solution. Placed in oxygen.
- " 16. 1.0 c.c. clear urine, containing urea, sulphates, and chlorides. Frog lively. *Post-mortem*: Viscera not pale. Rectum empty. Washed out and injected the vascular system. Microscopically: no injected glomeruli; epithelium normal in appearance.

Experiment 6.

- Nov. 17. Usual operation. Some hæmorrhage at operation. Emptied bladder and tied anus. Injected 2 c.c. urea solution. Placed in oxygen.
- " 18. No urine. Tied anus. Injected 2 c.c. urea solution. Oxygen.
- " 19. No urine. Tied anus. Injected 2 c.c. urea solution. Oxygen.
- " 20. 0.5 c.c. clear urine. Frog fairly lively. *Post-mortem*: Viscera pale and much blood-stained fluid found in the peritoneal cavity. Rectum empty. Washed out and injected vascular system. Microscopically: no injected glomeruli; epithelium normal in appearance. Urine contained urea, chlorides, and sulphates. Gave a reddish colour with picric acid and caustic soda, similar to that given by solutions containing kreatinin. Phosphates and urates could not be demonstrated. Reaction was about neutral to neutral litmus paper. Acidity to phenolphthalein: 1 vol. urine + 1.9 vol. $\frac{N}{100}$ NaOH was just alkaline to phenolphthalein.

Experiment 7.

- Nov. 28. Usual operation. Very little hæmorrhage at operation. Emptied bladder and tied anus. Injected 2 c.c. urea and dextrose solution. Placed in oxygen.
- " 29. Injected 2 c.c. dextrose and urea solution. Oxygen.
- " 30. 0.5 c.c. clear urine. Frog appeared moribund. *Post-mortem*: Rectum empty. Viscera were of normal colour. Washed out and injected vascular system. Microscopically: no glomeruli injected; epithelium normal in appearance. Urine reduced Fehling's solution readily. It contained urea, chlorides, and sulphates, and was neutral to neutral litmus paper.

Experiment 8.

- Dec. 5. In addition to the usual operation the rectum was ligatured above the bladder. Very little hæmorrhage at the operation. Emptied bladder and tied anus. Injected 2 c.c. phloridzin and urea solution. Placed in oxygen.
- " 6. Injected 2 c.c. phloridzin and urea solution. Oxygen.
- " 7. 0.5 c.c. clear urine. Tied anus. Injected 2 c.c. phloridzin and urea solution. Frog lively, but rather œdematous. Placed in oxygen. Urine reduced Fehling's solution readily, and gave a red colour, with a solution of ferric chloride. It contained urea, sulphates, and chlorides. It gave a red colour with picric acid and caustic soda. Phosphates and urates could not be demonstrated. Acidity to phenolphthalein. 1 vol. urine + 2.0 vols. $\frac{N}{100}$ NaOH was just alkaline.
- " 8. No urine. Frog moribund. *Post-mortem*: Viscera not pale. Rectum empty. Frog generally œdematous. Washed out and injected vascular system. Microscopically: no glomeruli injected; epithelium normal in appearance.

Experiment 9.

- Dec. 5. In addition to the usual operation the rectum was ligatured above the bladder. Very little hæmorrhage at the operation. Emptied bladder and tied anus. Injected 2 c.c. urea solution. Placed in oxygen. Urine drawn off at the time of the operation was alkaline to neutral litmus paper, and became alkaline to phenolphthalein on the slightest addition of $\frac{N}{100}$ NaOH.
- " 6. No urine. Tied anus. Injected 1 c.c. Na_2HPO_4 solution and 1 c.c. urea solution. Oxygen.
- " 7. 0.5 clear urine. Tied anus. Injected 1 c.c. Na_2HPO_4 solution and 1 c.c. urea solution. Frog lively, but rather œdematous. Placed in oxygen. Urine contained urea, chlorides, and sulphates. Gave a red colour with picric acid and caustic soda. It neither reduced Fehling's solution nor gave a reaction with ferric chloride. Phosphates and urates could not be demonstrated in it. Acidity to phenolphthalein: 1 vol. urine + 2.4 vols. $\frac{N}{100}$ NaOH just alkaline.
- " 8. 0.25 urine. Frog lively, but œdematous. *Post-mortem*: Viscera not pale. Rectum empty. Washed out and injected vascular system. Microscopically: no glomeruli injected; epithelium normal. Urine. Acidity to phenolphthalein: 1 vol. urine + 2.5 vols. $\frac{N}{100}$ NaOH just alkaline.

Experiment 10.

- Nov. 18. Usual operation. Very little hæmorrhage at the operation. Emptied bladder and tied anus. Injected 2 c.c. phloridzin and urea solution. Placed in oxygen.
- " 19. No urine. Tied anus. Frog lively. Injected 2 c.c. phloridzin and urea solution. Oxygen.
- " 20. No urine. Tied anus. Frog lively. Injected 2 c.c. phloridzin and urea solution. Oxygen.

- Nov. 21. One drop of clear urine drawn off from bladder. Frog lively and not œdematous. *Post-mortem*: Bladder and rectum empty. Viscera not pale. Washed out and injected vascular system. Microscopically: no glomeruli injected; epithelium normal in appearance.

Experiment 11.

- Dec. 1. Usual operation. A little arterial hæmorrhage at operation. Emptied bladder and tied anus. Injected 2 c.c. phloridzin and urea solution. Placed in oxygen.
- " 2. Injected 2 c.c. phloridzin and urea solution. Oxygen.
- " 3. Two drops of urine found in bladder. Frog fairly lively. Tied anus. Injected 2 c.c. phloridzin and urea solution. Oxygen.
- " 4. No urine. Frog appeared to be moribund and was slightly œdematous. *Post-mortem*: Bladder and rectum empty. Viscera not pale. Washed out and injected vascular system. Microscopically: no glomeruli injected; epithelium normal in appearance.

Experiment 12.

- Nov. 23. Usual operation. Very little hæmorrhage at the operation. Emptied bladder and tied anus. Injected 2 c.c. phloridzin and urea solution. Placed in oxygen.
- " 24. No urine. Tied anus. Injected 2 c.c. urea solution. Oxygen.
- " 25. Three drops of urine in bladder, which gave no reaction with ferric chloride. Tied anus. Injected 2 c.c. phloridzin and urea solution. Oxygen.
- " 26. One drop of urine in bladder. *Post-mortem*: Much blood-stained fluid in peritoneal cavity. Viscera pale. Bladder and rectum empty. Washed out and injected vascular system. Microscopically: no glomeruli injected; epithelium appeared normal.

Experiment 13.

- Nov. 24. Usual operation. Some arterial and venous hæmorrhage at the operation. Emptied bladder and tied anus. Injected 2 c.c. phloridzin and urea solution. Placed in oxygen.
- " 26. No urine. Tied anus. Frog lively but œdematous. Injected 2 c.c. phloridzin and urea solution. Oxygen.
- " 27. No urine. Frog very œdematous. *Post-mortem*: Bladder empty. Viscera rather pale. Washed out and injected vascular system. Microscopically: no glomeruli injected; epithelium appeared normal.

Experiment 14.

- Dec. 9. In addition to the usual operation the rectum was ligatured above the bladder. Very little hæmorrhage at operation. Emptied bladder and tied anus. Injected 2 c.c. urea solution. Placed in oxygen.
- " 10. Injected 2 c.c. urea solution. Frog fairly lively. Oxygen.
- " 11. No urine. Tied anus. Frog lively. Injected 1 c.c. urea solution and 1 c.c. Na_2HPO_4 solution. Oxygen.
- " 12. No urine. Frog feeble and rather œdematous. *Post-mortem*: Viscera not pale. Bladder and rectum empty. Washed out and injected vascular system. Microscopically: no glomeruli injected; epithelium appeared normal.

Experiment 15.

- Dec. 1. Usual operation. Slight venous hæmorrhage at operation. Emptied bladder and tied anus. Injected 2 c.c. normal salt solution. Placed in oxygen.
- " 2. Injected 2 c.c. normal salt solution. Oxygen.
- " 3. No urine. Tied anus. Frog lively but rather œdematous. Injected 2 c.c. normal salt solution. Oxygen.
- " 4. Five drops of rather blood-stained urine in bladder, which contained urea. Frog very œdematous. *Post-mortem*: Much blood-stained fluid in peritoneal cavity. Viscera pale. Bladder and rectum empty. Microscopically: no glomeruli injected; epithelium normal in appearance.

Experiment 16.—1906.

- Mar. 13. Tied both ureters and the rectum above the bladder and tied anus. Injected 2 c.c. urea solution. Placed in air.
- " 14. Injected 2 c.c. urea solution.
- " 15. No urine. *Post-mortem*: Bladder and rectum empty. Ureters and rectum properly ligatured.

Experiment 17.

- Mar. 13. Tied both ureters and the rectum above the bladder. Emptied bladder and tied anus. Injected 2 c.c. urea solution. Placed in air.
- " 14. Injected 2 c.c. urea solution.
- " 15. Injected 1 c.c. urea solution and 1 c.c. Na_2HPO_4 solution.
- " 16. Injected 2 c.c. phloridzin and urea solution.
- " 17. No urine. Frog lively, but rather œdematous. *Post-mortem*: Bladder empty. Rectum above colon contained a few drops of a brown fluid with numerous brown flakes in it. Ureters and rectum properly ligatured.

Experiment 18.

- Feb. 9. Normal frog. Emptied bladder and tied anus. Placed in oxygen throughout the experiment.
- " 10. 0.25 c.c. clear urine. Acidity to phenolphthalein; 1 vol. urine + 2.3 vols. $\frac{N}{100}$ NaOH just alkaline. Injected 1 c.c. Na_2PO_4 solution. Tied anus.
- " 11. 2 c.c. clear urine, which contained urea, chlorides, and sulphates. Phosphates and urates could not be demonstrated. It did not reduce Fehling's solution nor give any reaction with ferric chloride. Acidity to phenolphthalein: 1 vol. urine + 2.9 vols. $\frac{N}{100}$ NaOH just alkaline. No injection. Tied anus.
- " 12. 1 c.c. clear urine. Acidity to phenolphthalein: 1 vol. urine + 0.6 vol. $\frac{N}{100}$ NaOH just alkaline.
- " 14. 4.5 clear urine. This did not reduce Fehling's solution nor give a reaction with ferric chloride. Acidity to phenolphthalein: 1 vol. urine + 0.2 vol. $\frac{N}{100}$ NaOH just alkaline. No injection. Tied anus.
- " 15. 2 c.c. urine. Acidity to phenolphthalein: 1 vol. urine + 0.3 vol. $\frac{N}{100}$ NaOH just alkaline. Injected 1 c.c. Na_2HPO_4 solution. Tied anus.
- " 16. 1.5 urine, which did not reduce Fehling's solution. Acidity to phenolphthalein: 1 vol. urine + 1.5 vols. $\frac{N}{100}$ NaOH just alkaline. Tied anus.

- Feb. 18. 0.25 c.c. urine. Acidity to phenolphthalein: 1 vol. urine + 0.4 vol. $\frac{N}{100}$ NaOH just alkaline. Injected 1 c.c. urea solution. Tied anus.
- " 19. 0.75 c.c. urine. Acidity to phenolphthalein: 1 vol. urine + 0.4 vol. $\frac{N}{100}$ NaOH just alkaline. Injected 1 c.c. Na_2HPO_4 solution. Tied anus.
- " 20. 3.5 urine. Acidity to phenolphthalein: 1 vol. urine + 0.5 vol. $\frac{N}{100}$ NaOH just alkaline.

Experiment 19.

- Feb. 21. Normal frog. Emptied bladder and tied anus. Placed in air throughout experiment.
- " 22. 1 c.c. urine which did not reduce Fehling's solution. Injected 1 c.c. dextrose solution (1 g.). Tied anus.
- " 23. 2.5 urine, which gave no reaction with ferric chloride. The sugar was estimated in this by Pavy's method. 2.3 per cent. dextrose was found, which in 2.5 urine would amount to about 0.06 g. No injection. Tied anus.
- " 24. 2 c.c. urine, which gave a slight reduction with Fehling's solution.

Experiment 20.

- Feb. 23. Normal frog. Emptied bladder and tied anus. Placed in air throughout experiment.
- " 24. 1 c.c. urine, which neither reduced Fehling's solution nor gave a reaction with ferric chloride. Injected 2 c.c. phloridzin and urea solution. Tied anus.
- " 25. 2.5 c.c. urine, which was acid to neutral litmus paper, and gave a red colour with ferric chloride. It contained 0.21 per cent. dextrose estimated by Pavy's method. The injections of phloridzin were continued for a week. The urine contained dextrose throughout. On the fifth day severe diarrhoea was set up.

Experiment 21.

- Feb. 7. Usual operation. Very little hæmorrhage at operation. Emptied bladder and tied anus. Injected 1 c.c. urea solution. Placed in oxygen.
- " 8. 1 c.c. urine. Frog very sluggish, probably due to cold weather, possibly to hæmorrhage. *Post-mortem*: Much blood in the peritoneal cavity. Viscera pale. Washed out and injected the vascular system. Microscopically: no glomeruli injected except at the extremities of both kidneys where numerous glomeruli contained the injection; epithelium normal.

Experiment 22.

- Feb. 24. Usual operation. Very little hæmorrhage at operation. Emptied bladder and tied anus. Injected 1 c.c. dextrose solution and 1 c.c. urea. Placed in oxygen.
- " 25. 0.5 c.c. urine, which reduced Fehling's solution strongly. Tied anus. Injected 1 c.c. dextrose solution and 1 c.c. urea solution. Oxygen.
- " 26. Few drops of urine which reduced Fehling's solution. *Post-mortem*: Viscera not pale. Washed out and injected vascular system. Microscopically: no glomeruli injected except at the anterior end of both kidneys; epithelium normal.

TWO CASES OF MALIGNANT EMBRYOMA OF THE OVARY.

READ BY J. H. TARGETT, M.S., F.R.C.S.,

AND

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Before the Obstetrical Society of London.

As this form of ovarian tumour is very rare, and as no similar case has been brought before this Society, we have ventured to place on record a short account of a characteristic example of the disease, and to include references to the recent literature of the subject. Such growths are usually included in the group of teratomata, but, on account of their close relationship to the so-called dermoid tumours of the ovary, we prefer the title of "malignant embryoma."

CASE 1.—Emily E., æt. 14, was admitted into Guy's Hospital on December 21st, 1903. She was taken suddenly ill on the day before admission with severe abdominal pain and sickness. Previous to this attack she had been in her usual condition of health, but had always been thin and delicate (her parents were dead, the cause of death not being known). She was at work at a paper bag factory up to the time of the attack. The bowels were open on the day before admission, and there was a history of vaginal discharge for about a month. She had reached puberty, and had menstruated once. The period lasted three days, and was normal.

On admission she was in great pain, her pulse 128, her temperature 102°, her tongue dry and furred. On examination the abdomen was slightly distended, rigid at its lower part, with a little tenderness on palpation. The flanks and upper part of the abdomen were resonant, but there was dulness from the umbilicus to the pubes, where an indefinite thrill could be obtained. *Per vaginam*, a cystic swelling could be felt high up and to the left of the uterus. It was, however, difficult to carry out a satisfactory bimanual examination on account of the rigidity of the abdominal wall. The signs and symptoms suggested peritonitis—a diagnosis which was made all the more probable by the presence of the vaginal discharge. After resting in bed for a few hours, her pulse became slower, and the temperature came down to 99·4°. The diagnosis was then altered to one of ovarian tumour, with torsion of the pedicle and peritonitis.

Mr. Targett opened the abdomen in the middle line, and immediately came upon a black ovarian tumour with many recent adhesions to the anterior abdominal wall, and more firm attachments to the omentum above. The tumour was tapped, but only a little dark, blood-stained material came away. An incision was then made into the mass, and a large handful of semi-solid necrotic material was evacuated. The capsule was so rotten that it broke into small pieces during removal, but the whole mass was at length got away, and proved to be a left-sided ovarian tumour, the pedicle of which had two and a half twists. The abdominal cavity was washed out with normal saline solution, and the abdominal wall sewn up with salmon-gut sutures. The patient did very well after the operation, the pain ceased, and the temperature came down to normal.

She went out on January 24th, 1904, to a convalescent home; the abdominal wound was quite healed, and the patient had increased considerably in weight. Menstruation became regular, and the patient remained well for three months. She then began to complain of abdominal pain, which was soon followed by swelling. She was readmitted on May 14th, 1904, suffering from well-marked ascites and rapid wasting. A large mass could

be felt in the left iliac fossa. The abdomen was again opened by a small incision, and a large quantity of serous fluid evacuated. Sessile and pedunculated growths were found studded over the intestines and omentum. The large mass of growth in the left iliac fossa was found to be firmly fixed, and to extend deeply into the pelvic cavity. Further operation being impossible, the abdomen was again washed out and sewn up. Within fourteen days the ascites recurred and the abdomen had to be tapped. Subsequently paracentesis was performed five times, but the patient went steadily downhill. She wasted quickly, her temperature became irregular and pyrexial, the urine alkaline and purulent, and she died, in a condition of uræmic coma, seven months after the first operation.

At the first laparotomy there was no ascites, nor were there any secondary growths seen on the peritoneum. The primary tumour was almost black in colour, and about the size of a man's head. There was a distinct pedicle, which was tightly twisted. The whole mass looked like a cystic adenoma of the ovary, which had become necrotic and discoloured as the result of torsion of its pedicle, but, as was noted at the time of the operation, there was a considerable amount of solid material present in the tumour. It is impossible to give a more detailed account, for the tumour was so rotten that it had to be removed in pieces.

The appearance of the peritoneum at the second operation was practically the same as that found at the *post-mortem* examination.

Autopsy, July 1st, 1904. The following appearances were noted :—

Great wasting of the body. Laparotomy wound healed. Lungs—septic bronchopneumonia and pleuritic adhesions at both bases. No growth found. Heart normal. The pericardium held a small quantity of serum.

The peritoneal cavity contained 62 oz. of blood-stained fluid. The parietal layer was thickened and white, with numerous growths on its surface. The stomach was normal, and free from growth on its peritoneal surface. The lumen of both small and large intestines was not encroached upon, nor the mucous

membrane infiltrated by growth; but upon the peritoneal aspect of these parts there were numerous masses, varying in size from a pin's head to an orange. These growths formed in many places pedunculated masses, similar secondary growths being seen on the capsule of the liver and spleen. The striking point about these deposits was the superficial manner of their growth.

The main mass of the recurrent growth was found in the pelvis, being situated more on the left side. The uterus was buried in it, and the right ovary was the seat of a nodular growth, about the size of a tangerine orange.

The recurrent tumour measured 11 inches in the vertical, extending upwards almost to the lower pole of the left kidney. The transverse diameter was about seven inches, and the antero-posterior six inches. The kidneys were in a condition of suppurative nephritis; the mucous membrane of the ureters and the bladder was inflamed, but the ureters were not dilated.

The growth was white in colour, and its surface coarsely nodular. On section the cut surface presented a white appearance, with small hæmorrhages here and there into its substance. Each lobulated mass consisted of a central core of white fibrous tissue, and from this centre septa ran towards the periphery, and contained between these septa was growth of softer consistency. Although for the most part the tumour appeared solid, there were in many places cystic spaces, varying greatly in size. No cartilage, bone, or hair could be seen with the naked eye. Many of the retro-peritoneal lymph-glands were apparently infected, but on account of the extreme alteration of the anatomical disposition of the peritoneum by the growth, it was difficult to be precise in distinguishing between retro-peritoneal and intra-peritoneal deposits.

Microscopical examination.—The sections taken both from the primary and secondary growths may be roughly described as composed of:—

- (1) Tubules and cysts of various kinds.
- (2) Nodules of cartilage and bone.
- (3) Epithelial pearls; and
- (4) A groundwork of fibrous, muscular and fatty tissues.

A short description of each of these elements will be given.

(1) *Tubules and cysts.*—These are very numerous, and their shapes and sizes vary greatly. Some are lined with tall columnar epithelium, like that of the large intestine, and the resemblance to bowel is increased by the presence of bands of unstripped muscle arranged irregularly around them. Certain tubules of this class are distended with mucoid secretion and form small cysts. A second variety may be termed acini, and these are in clusters like mucous glands; here and there they are in close apposition with nodules of cartilage, recalling the structure of bronchial tubes. A third type may be described as cystic spaces lined partly with columnar and partly with squamous stratified epithelium, the change from the one to the other kind of epithelium being curiously abrupt. Lastly, a few tubules were probably lined with columnar ciliated epithelium, as the arrangement of the cells resembles that in the respiratory muscles.

(2) The nodules of *cartilage* are small, and are oval or spherical on section. They are all composed of hyaline cartilage, and most of them possess a thin capsule of condensed fibrous tissue. A few fragments of bone may be seen, and they do not appear to be calcified cartilage, but irregular plates of ossification in the fibrous stroma.

(3) The *epithelial pearls* are striking objects in the sections. They exhibit a single layer of cubical epithelium at the periphery, and this is succeeded by a dozen or more layers of somewhat flattened or fusiform cells concentrically arranged. The central cells retain their nuclei, but are evidently becoming degenerated and swollen. A similar arrangement of cells is seen in the spaces lined with stratified epithelium, and it may be that some of the pearls represent transverse sections of such spaces.

(4) The *groundwork* of the tumour has a complex structure. In it may be recognised simple adipose tissue, broad bands of unstripped muscle-fibres, gelatinous areas like foetal connective tissue, much denser fibrous material, fields of a delicate granular substance like neuroglia, and finally a sarcomatous growth composed of round and small fusiform cells. Groups of ganglion cells like those of the sympathetic system in the intestinal wall

may also be seen between the bundles of muscle. In spite of the abundance of these constituents, there is no anatomical arrangement of the parts to form a definite organ; the derivatives of the primary germinal layers seem merely to have run to waste.

CASE 2 (under the care of Mr. Reynall Bellamy, in Stockport Infirmary, to whom we are greatly indebted for the clinical notes).—A child (female), æt. 6, admitted with swelling of the abdomen, which had been noticed for three weeks. After tapping the abdomen a tumour was found extending from the pelvis into the abdominal cavity. This was removed by abdominal section without great difficulty, but within three weeks the ascites had recurred, and after several abdominalappings the patient died, about two months from the first operation.

No *post-mortem* examination was allowed.

The primary tumour was about the size of a cricket-ball; it was rounded, but slightly irregular in shape, and the outer aspect of the capsule was for the most part smooth and free from adhesions.

The fimbriated end of the Fallopian tube was attached to the lower pole of the tumour, and, together with a small portion of the broad ligament, formed a definite pedicle.

On section the mass was found to be of an almost uniform chocolate colour, due to hæmorrhage into it at every part. Its substance was of a soft friable nature, with many cystic spaces, varying in size from that of a pin's head to a walnut. The mass was in such a degenerated condition that it easily broke down under the finger, and it was only by taking numerous pieces for section that a definite histological structure could be made out. The slides prepared showed cartilage and similar cystic spaces to those observed in the present specimen. This tumour was chiefly composed of round and small spindle-shaped sarcomatous cells. A capsule formed of condensed ovarian tissue could be recognised in some of the sections. Unfortunately, no secondary growths were available for examination. The details thus lack completeness, but are interesting as relating to the youngest known case on record.

Remarks.—The number of recorded cases of malignant embryomata is small. Säger, writing in Martin's "Gynæcology," says there are fourteen published cases, and Pfannenstiehl puts the number at ten. With eleven collected from the literature added to our own two we have thirteen cases. The microscopical appearances described by Pfannenstiehl, Emmanuel, Säger, Lazarus, Ewald, and others correspond closely with our own sections, though in some instances a larger amount of nervous tissue was found. In Backhaus's case large patches of embryonic brain substance, neuroglia, and ganglion cells are described. Saxer also found nervous tissue. On the other hand, Emmanuel and Kramer failed to find any evidence of nervous structures. Hair-follicles, sweat-glands, and pigment have also been met with in some specimens. Krömer describes an embryonic retina in close relation to patches of pigment. No doubt the individual germinal elements vary in the extent of their development in different specimens. Gsell states that ectodermic structures were absent in his case. Wilms has found that the three primary germinal layers are often represented in the solid processes (Zotte) of many dermoid cysts of the ovary, but states that the ectodermic elements are by far the most developed. Beneath the ectodermic structures may be seen plain muscular fibres, cartilage, and other mesodermic derivatives, and lying below these may also be seen tubular spaces, lined with columnar epithelium, which are taken to be endodermic in origin. Thus there seems to be a close relationship between the ordinary innocent dermoid cyst of the ovary and the very mixed tumour which we think is best called malignant embryoma.

Metastases.—There is a tendency for metastatic growths to confine themselves to the peritoneum and retro-peritoneal lymph-glands, visceral metastases being rare, and only mentioned in less than one-third of the cases. The pleura was found infected in Kramer's case, as well as the peritoneum. In Falk's case there were metastatic growths in the lungs, and in the case described by Backhaus the patient died with symptoms of cerebral tumour, and large secondary growths were present on

each side of the neck. In this case, however, there was no *post-mortem* examination, but the primary growth was a typical mixed embryoma. Sanger draws attention to the frequency of peritoneal infection, and he looks upon the secondary growths as implantation grafts. Ewald comes to the same conclusions. The tendency, therefore, is for the secondary growths to confine themselves to the peritoneum, but general dissemination occurs in a few cases.

As regards the microscopic appearance of the secondary growths, there seem to be two distinct varieties. In our first case, and in those given by Emmanuel, Lazarus, Ewald, and Falk, the secondary growths were of the same complicated nature as the primary growth, but in the cases of Keller, Saxer, and Kramer the metastases were of the type of the small, round-celled sarcoma; in these latter cases the mesoblastic elements only seem to have become disseminated.

The recurrent growth in the pelvis may reach an enormous size, in our first case measuring 11 by 7 by 8 inches.

It is difficult to discuss the question of malignancy, because a hard and fast line cannot be drawn between the complex dermoids and malignant embryomata. Perhaps it is legitimate to look upon these growths as bearing the same relation to one another as the benign and malignant adenomata—that is, to speak of benign and malignant dermoid tumours of the ovary.

The large size of the solid primary tumour, and the extreme confusion of the elements of the germinal layers, would constitute the distinguishing features.

However, Kroemer records a growth, possessing the size and microscopical appearance of a malignant embryoma, where the patient was well and free from recurrence a year after operation.

If we are provisionally to regard this case as innocent, we must reserve our ultimate opinion as to the invariably malignant character of these mixed embryomata. But 11 undoubted malignant cases are on record; 9 of these died within the year, Ewald's case lived 1½ years, and Falk's 2½ years. Lazarus's patient died a few days after operation.

The patients, three of whom were multipara, were all under 30 years, the respective ages at death being 6, 13, 14, 15, 17, 20, 20, 21, 22, 27 and 30 years.

From the consideration of these cases, the following conclusions may be drawn :—

(1) Malignant embryomata of the ovary are rare. They usually occur in young adults, but may be met with in childhood.

(2) The tumours may attain a large size; they are usually pedunculated, and devoid of adhesions unless the pedicle has become twisted.

(3) Secondary growths are frequently restricted to infection of the peritoneum. They may present the same composite structure as the primary growth, or be wholly composed of sarcomatous elements.

(4) Pain and ascites are constant symptoms; ascites may develop early, even before actual infection of the peritoneum. In several instances a diagnosis of twisted ovarian cyst has been made.

(5) Ovarian tumours exhibiting an irregular disposition of embryonic elements are very liable to be malignant.

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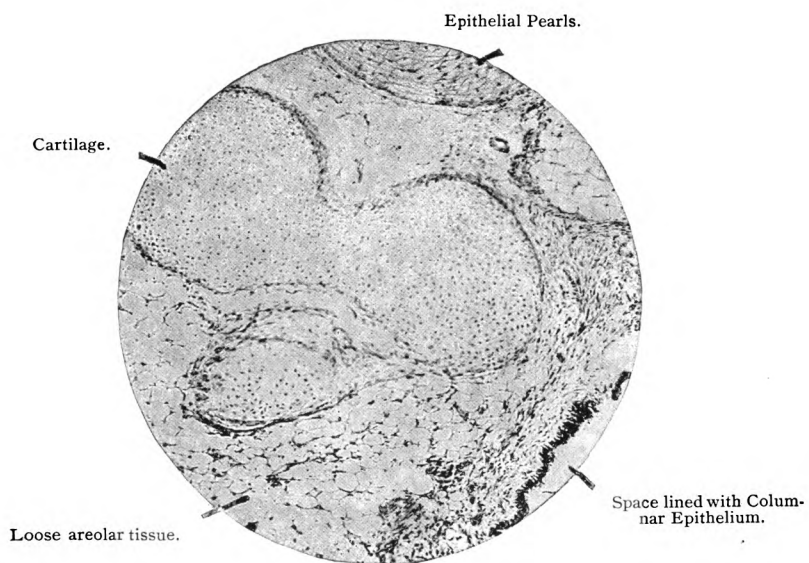
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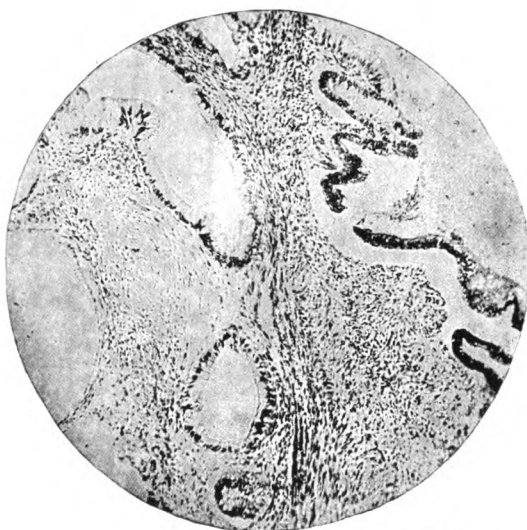
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Two Cases of Malignant Embryoma of the Ovary.



Micro-photo by Dr. HIGSON.

Two Cases of Malignant Embryoma of the Ovary.

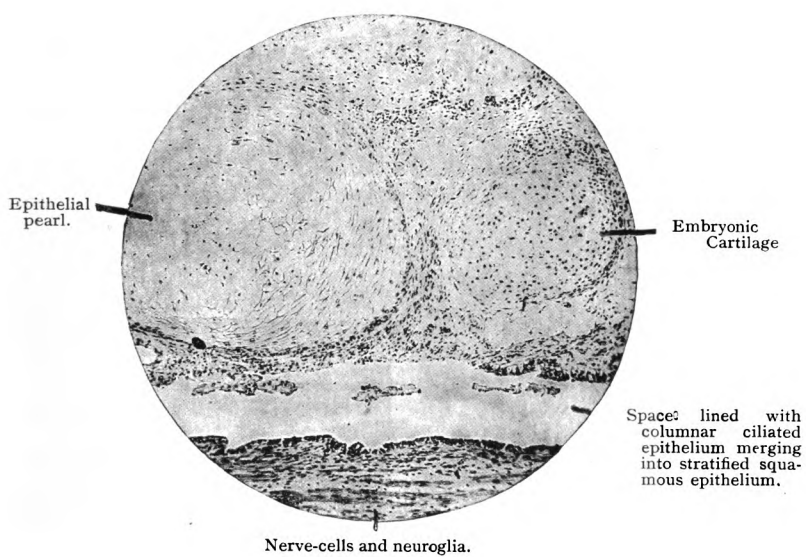


Cystic space lined
with tall cylindri-
cal epithelium.

Nervous elements.

Micro-photo by Dr. Higson.

Two Cases of Malignant Embryoma of the Ovary.



Micro-photo by Dr. HIGSON.

A NOTE UPON THE RELATION OF TRAUMATIC DIABETES INSIPIDUS TO GLYCOSURIA.

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THE following is an addition to the history of that case which was published in Vol. LVII. of the Guy's Hospital Reports, under the title: "A Research upon the Metabolism of a Patient suffering from Diabetes Insipidus, following upon Fracture of the Skull."

The notes of the case at the time of the last publication are briefly as follows:—William T., aged 44, was in perfect health up to June, 1901. He then met with a bicycle accident, fracturing his basisphenoid. He was unconscious for fourteen days, cerebrospinal fluid dripping from his nose. He recovered, and became active and able to resume work; but suffered from bilateral temporal hemianopia, slight strabismus, polydipsia, and polyuria, all attributable to his head injury.

His condition was typical of diabetes insipidus. He was under close observation from September 12th to October 15th, 1901, during which time all his food and drink were strictly measured and analysed, as were also his urine and fæces. He passed, upon the average, 7,500 c.c. of urine daily, of specific gravity 1004. He drank fluids proportionately. The urine was daily examined for sugar, but on no occasion could any be found.

Not only did the man not pass sugar in his urine when he was taking ordinary diet, but he could not be made to pass sugar when his carbohydrate diet was abnormally increased. Upon different occasions he was given excess of lactose, of grape-sugar, of cane-sugar, and of starch. His daily consumption was pushed until he was taking over 700 grams of dry carbohydrate in addition to the ordinary amount of proteid and of fat, yet no sugar appeared in his urine at that time. His diabetes insipidus seemed then to be quite free from any tendency to glycosuria.

The history of the case, subsequent to the metabolic research carried out in 1901, is interesting in that the patient has now spontaneously developed a glycosuria which at that time could not be dietetically produced. During 1902 and 1903 the man remained actively at work as an insurance agent, suffering from no inconvenience except his impairment of sight and his continued polydipsia and polyuria. He ate well, and maintained his vigour and weight. In September, 1904, his medical attendant detected a small amount of sugar in his urine for the first time—three years and four months after his fractured base and the onset of diabetes insipidus. Notwithstanding treatment, the glycosuria persisted. The man did not suffer any change of symptoms, and did not lose weight, nor relinquish his work. In February, 1905, he came into Guy's Hospital again, under the care of Dr. Beddard (Medical Report, No. 124). In his general condition he was much the same as upon his discharge in 1901. His weight had not altered; he had the same slight strabismus, the same bilateral hemianopia, the same polydipsia. His heart, lungs, abdominal organs, and general nervous system seemed perfectly healthy.

The condition of his urine is the main point of interest. Whilst upon ordinary diet, analyses showed :—

Date.	No. of ounces of Urine passed in each 24 hours.	Specific gravity.	Reaction.	Percentage of sugar.	Total sugar in grains per 24 hours.	Diacetic acid (ferric chloride test).	Acetone (sodium nitroprusside test).
Feb. 21	100	1016	Neutral	4.76	2080	Not found	Not found
Feb. 27	106	1016	Neutral	2.63	1220	Not found	Not found
Feb. 28	172	1016	Neutral	3.57	2687	Not found	Not found
Mar. 1	243	1016	Neutral	2.84	3020	Not found	Not found
Average	155	1016	Neutral	3.45	2252	Not found	Not found

The sugar was estimated by Pavy's method; and was shown to be glucose both by the fermentation test and by the formation of phenylglucosazone crystals.

The patient was then put upon the strictest diabetic diet, and the urine analyses for a week afterwards were as follows :—

Date.	No. of ounces of Urine passed in each 24 hours.	Specific gravity.	Reaction.	Percentage of sugar.	Total sugar in grains per 24 hours.	Diacetic acid (ferric chloride test).	Acetone (sodium nitroprusside test).
Mar. 2	179	1016	Neutral	2.02	1580	Not found	Not found
Mar. 3	222	1014	Neutral	0.83	809	Not found	Not found
Mar. 5	186	1010	Neutral	0.87	706	Not found	Slight
Mar. 6	206	1010	Neutral	0.54	483	Not found	Slight
Mar. 7	188	1010	Neutral	0.27	219	Not found	Not found
Mar. 8	193	1010	Neutral	0.25	209	Not found	Slight
Mar. 9	196	1010	Neutral	0.35	270	Not found	Slight
Mar. 10	202	1010	Neutral	0.48	489	Not found	Slight
Average	200	1011	Neutral	0.70	596	Not found	Slight

Thus the sugar fell to one quarter of what it was upon ordinary diet; but the man who, in 1901, could not be made to pass sugar

in his urine when he had carbohydrate pushed to nearly double what an ordinary man takes, in 1905 failed to assimilate properly the minimal amount that a strict diabetic diet contains. The restricted diet was carefully continued for a much longer period, but sugar was persistently present in the urine.

It is not within the province of the present note to discuss whether or not there be a fundamental distinction between "alimentary glycosuria" and "true diabetes mellitus." The difference may be one of degree only. It is, however, recognised that some cases of glycosuria are simpler than others; and that in the simpler cases there is usually no diacetic acid or acetone in the urine, whilst the glycosuria disappears when the carbohydrate food is strictly limited. It was thought that the present case was possibly a simple alimentary glycosuria, and that strict dieting would cause a disappearance of the sugar from the urine. We were a little surprised that this did not turn out to be the case. We lay no stress upon the occurrence of acetonuria, because it has been found that a perfectly sound man will pass acetone in his urine if all the carbohydrate be eliminated from his food. Our patient's urine was by no means typical of diabetes mellitus; diacetic acid was never found; the specific gravity was low. Nevertheless the fact that the sugar did not disappear entirely upon careful dieting would seem to show that the condition was not "simple" nor purely "alimentary," though the patient maintained his weight and felt quite fit for work.

Brouardel and Richardière (1) have written an exhaustive paper upon the relation of injury to diabetes mellitus, from a medico-legal point of view. They could find only 33 cases in which injury could be put down as a factor in the causation of glycosuria. The injuries in their cases were by no means always to the head. Of their 33 collected cases:—

17 were secondary to head injuries.

5 " " injury to the spine.

11 " " injury to various parts of the body

In regard to the time after the injury at which glycosuria was discovered :—

In 8 cases there was glycosuria within 2 days of the injury.

" 4	"	"	7	"
" 5	"	"	3 to 6 weeks	of the injury.
" 3	"	"	2 months	"
" 2	"	"	3 months	"
" 1	"	"	4 to 5 months	"
" 9	the intervals were longer still, up to 4 years			

They give examples of every degree of glycosuria secondary to injury. In some the condition was temporary, rapidly getting well by itself ; in others, careful treatment was required, but cure resulted ; in others again the glycosuria persisted in spite of treatment, but the condition seemed to be stationary, and did not seriously affect the patient ; finally, there were those bad cases which ran the ordinary course of rapid diabetes mellitus with a fatal ending. Nevertheless, they lay stress upon the rarity with which diabetes can be attributed to injury. Griesinger (4) holds the same view after analysing 225 cases, amongst whom he found only 20 in which trauma could by any possibility be put down as a cause. Senator (6), having collected 1,090 cases of diabetes mellitus, could find but 11 cases, or 1 per cent., in which he could definitely attribute the condition to any injury.

The question of the relation of head injury to diabetes mellitus has been discussed in a previous paper (2) ; in which, and in a paper by Fletcher (3), references to the literature are given. The conclusions drawn are, that head injury rarely causes either form of diabetes, but that diabetes insipidus is attributable to injury rather less infrequently than is diabetes mellitus.

The majority of cases of diabetes insipidus are not associated with glycosuria. Some Guy's Hospital cases (2) have had diabetes insipidus for many years without becoming seriously ill, and without developing glycosuria. When, however, it is so well established that Claude Bernard's puncture of the fourth ventricle leads to glycosuria, and when it is recognised that injuries and tumours of the base of the brain certainly may be a cause of polyuria, it is contrary to expectation that a head injury which

is followed by persistent diabetes insipidus should not also lead to glycosuria. Nevertheless, we have been able to find only one case in the literature which exactly resembled our own. This is recorded by Brouardel (1). A man, aged 45, met with a railway accident on July 18th, 1884. He was generally concussed, but did not lose consciousness. Twelve days later, on July 30th, 1884, it was noticed that his urine was "very much increased" in quantity, and that no sugar was present. He recovered, but continued to suffer from polyuria and excessive thirst. He was again examined on December 24th, 1884, when the polyuria with absence of sugar was confirmed. The same condition persisted through the greater part of the next year; but on November 30th, 1885, sixteen and a half months after the accident, he was found to be passing sugar to the extent of 47 grams per litre. The specific gravity of his urine was 1032, and the daily quantity "large." There is no mention of diacetic acid or of acetone having been tested for. The man's general health was good, and his condition appears to have been very similar to that of the present patient. In both cases polyuria immediately followed a severe accident affecting the brain; in both, the polyuria persisted; in both, there was absence of sugar for a long while after the accident; in both, sugar ultimately appeared in the urine, in Brouardel's case $1\frac{1}{2}$ years, in our case $3\frac{1}{2}$ years after the injury. In both cases the general health was excellent, notwithstanding accident, polyuria, and glycosuria.

In our search for other similar cases, we have come across one which is almost the converse. Kæmnitz (5) records it. A woman, aged 17, met with an accident in which her head became severely compressed amongst the wheels of some machinery. She was comatose, and the same day passed 500 c.c. of clear, non-albuminous urine, free from sugar. Six days later, being then conscious again, she complained of great thirst, and passed much pale urine, of specific gravity 1023, and containing 1 per 100 of sugar. Two weeks later the urine had a specific gravity of 1029, and there were 2.3 parts of sugar per 100. For one month the urine continued much the same; then the sugar began slowly to diminish. At the fourth month from the injury

there was no sugar in the urine, but the patient passed from 4000 c.c. to 6000 c.c. daily, of specific gravity 1005. This polyuria persisted. Sugar did not recur. The condition seems to have been one of traumatic polyuria and glycosuria, which passed on to one of simple diabetes insipidus.

In our previous paper we drew the conclusion that the head injury, which had caused diabetes insipidus in our patient, had in no way diminished his power of metabolising carbohydrate. It is true that this was the case at that time; but it seems important to record the fact that in the course of a few years a complete change occurred in this respect. The patient, in the early stage of his traumatic diabetes insipidus, had been able to assimilate enormous amounts of starch, glucose, lactose, and cane sugar; but after three and a half years ceased to be able to metabolise properly even quite small quantities.

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A year later, the glycosuria had as spontaneously ceased. The patient's weight had increased one stone. The polyuria and polydipsia persisted unchanged. The patient was shown personally to the Clinical Society on March 9th, 1906.

Our best thanks are due to Dr. Hale White, under whose care, at Guy's Hospital, the patient was, and is, and who has given us every facility in our observations.

(Read before the Obstetrical Society of London.)

THE FATE OF THE OVUM AND GRAAFIAN FOLLICLE IN PRÆ-MENSTRUAL LIFE.

By THOS. G. STEVENS, M.D.

It has been stated and apparently accepted as a fact that some Graafian follicles do not lie latent in the ovary from birth until puberty, and it has been suggested by Waldeyer,¹ Beigel,² and others that a process of ripening occurs, to be followed by atrophy and the formation of a kind of corpus luteum. The number of Graafian follicles contained in the ovaries at birth has been estimated at 70,000, and all observers are agreed that there are considerably less in the ovaries at puberty. The actual figures referred to must be viewed with some scepticism, because the enumeration of the Graafian follicles in an ovary cannot be a matter of any certainty, and there must be a large margin for errors of observation. However this may be, there is not the slightest vestige of a doubt that large numbers of Graafian follicles do disappear between birth and puberty. On the other hand, very few, if any, new follicles are formed after birth; sections of the ovaries of new-born children very seldom show ova and follicles in process of formation.

While the disappearance of Graafian follicles is accepted by all, the amount of literature actually bearing on this point is surprisingly small. A prolonged search through the papers dealing with work on young ovaries has not yielded much which throws any light on the method by which the ova and follicles disappear. De Sinéty³ describes infants' ovaries, which show all

stages of maturation up to what may be called ripeness (as far as præ-menstrual ovaries go), and although he mentions that retrograde changes occur, he does not make it clear how these take place. Slavianski⁴ is largely quoted in respect to retrograde changes in Graafian follicles, but all his papers deal with adult ovaries and the retrograde changes in certain Graafian follicles which fail to burst and discharge their ova. Schotlaender,⁶ too, describes well the development of the egg and follicle, but does not go deeply into the question of retrograde changes. One of Schotlaender's plates, however, is very interesting, as it shows an ovum with an included cell which corresponds closely with one of the stages of retrogression of the ovum which will be described in this paper. Schotlaender does not appear to have attached much importance to this specimen, except that he considered it worthy of record in a drawing. Paladino⁷ describes the atrophy of Graafian follicles and ova in young females, but apparently his specimens were obtained from females after puberty. Henneguy,⁸ in an interesting paper, goes fully into the retrograde changes in Graafian follicles in animals of various species; his specimens do not include those from human infants. However, one of his plates is interesting, as it shows an ovum with included cells something like the appearances to be described later. This ovum was not human. Balfour,⁹ too, shows an ovum with an included cell, but does not touch upon retrograde changes in infantile ovaries. Many other authors, among them Loewenthal,¹⁰ Virchow,¹¹ Cadiat,¹² Langhans,¹³ Pflüger,¹⁴ Laulanie,¹⁵ Pettitpierre,¹⁶ Nagel,¹⁷ Alexandrini,¹⁸ Van Spee,¹⁹ Von Kölliker,²⁰ McLeod,²¹ Van Beneden,²² Grohe,²³ have contributed excellent papers on the subject of the ovary in animals and human beings, but in none of them are the maturation and retrograde changes of Graafian follicles in infants fully described.

The researches, the subject of this paper, were undertaken to try and determine to what degree the Graafian follicle does mature in præ-menstrual life, and if possible to show the retrograde stages until a scar is formed, and also to show what becomes of the ovum during these retrograde changes. The

material for these investigations—upwards of seventy pairs of ovaries of children of various ages (but always under ten years, so as to eliminate the possibility of menstruation having been established)—was collected from the *post-mortem* rooms of Guy's Hospital and the Evelina Hospital for Sick Children, with occasionally specimens from other places sent by friends. The method of preparation of the earlier specimens was simple hardening in alcohol after cutting the ovary in two in its long axis. This was not found to be very satisfactory, and so the later specimens were fixed *whole* in saturated solution of corrosive sublimate and then the hardening carefully completed in alcohols of increasing strengths beginning at 30 per cent. and ending with absolute. In the earlier specimens it was found that hemisection of the ovary nearly always opened the larger follicles, which, of course, were the most important to keep entire, the contents nearly always being lost during section. When, however, the ovaries were hardened whole and embedded whole in paraffin good results were obtained, and the various stages of development to be described were almost always found. The human ovary is always a most difficult object to cut good serial sections of, and embedding them whole does not make the process any easier. However, by paying great attention to thorough dehydration and slow saturation with paraffin at as low a temperature as possible consistent with its melting point, it was found to be possible to cut good serial sections. There is no doubt that the results to be described depend entirely on the method of fixation and embedding; no complete series of changes in Graafian follicles can be obtained if the ovaries are first cut in half. One cannot but believe that this is the reason why these changes have not been previously completely described. Various stains were used for the sections, but on the whole hæmatoxylin and eosin or carmine and picro-nigrosin were found to give the best results. Eosin was found to be especially useful as a counter-stain in those specimens in which it was required to stain blood-vessels and blood-corpuscles.

Before describing the various steps by which the Graafian follicle matures and then gradually disappears, leaving a fibrous

scar, it may be said at once that no rupture of the follicle takes place, and nothing in the least approaching the structure of a corpus luteum is formed. The follicle and contained ovum matures up to a certain point by definite steps, then a kind of phagocytosis takes place by which the ovum is removed, and finally the contents of the follicle are absorbed by a species of granulation tissue which forms in its wall. From this granulation tissue new connective tissue is formed which gradually fills up the cavity and seems to contract as the cavity becomes less and less, at last nothing remains but a cicatrix with very few cellular elements in it.

It is not intended to touch upon the development of the Graafian follicle and primordial ova in this paper, the researches of Waldeyer¹ and Foulis,²⁴ which have been confirmed by many others, seem to be sufficiently convincing to require no further confirmation or criticism. But, nevertheless, it is interesting to note that in all these specimens there is little or no evidence of any actual formation of new Graafian follicles going on, and so it would appear that the oft-repeated statement is true in general, that all the ova are formed before or just after birth. If a complete section in the long direction of a child's ovary is examined it will be found at once that there are many follicles present in different stages of development. The youngest follicles will be found all over the surface of the ovary, and especially at the two ends, where many layers of follicles will be found, all at the same stage of development. As the follicle begins to enlarge it will be found deeper in the substance of the ovary. The largest follicles, sometimes as much as 5 mm. in diameter, approach the surface, not with a view to rupture, but simply because the ovary is not large enough to contain them otherwise. It is interesting to note that it is not uncommon to find quite young children's ovaries containing several very large follicles, for instance, the two (from different children) shown in Fig. 14, drawn three times their natural size. These are in no way pathological, and there is plenty of evidence to show that such large follicles do eventually contract without bursting, and finally form a fibrous scar. Such ovaries no doubt have often been

described as cystic, and have been looked upon as pathological erroneously.

The youngest Graafian follicles, those which may be termed dormant follicles, together with their contained ova, measure on an average $\cdot 0325$ mm., this measurement practically being that of the ovum itself, as the covering of the follicle consists at this stage of flattened cells only, closely applied to the ovum. There is no particular evidence here of a proper fibrous tunic to the Graafian follicle, and the flattened cells look like and stain in the same manner as the connective tissue cells of the ovary around them. The ovum usually shrinks a little away from the follicle, no doubt on account of the method of preparation of the specimen. The more carefully the ovaries are fixed before cutting sections the less shrinkage will be seen. At this stage there is no evidence of a zona radiata surrounding the ovum. The nucleus of the ovum measures on an average $\cdot 013$ mm. in diameter, and there is a well-marked nucleolus present (Fig. 1).

Fig 2 shows the first stage undergone by the dormant follicles towards maturation. The most marked change seen is that the flattened cells surrounding the ovum proliferate, the number of cells in the specimen shown being treble the average number in a dormant follicle. At the same time, the cells are altered in shape, so that they now assume a cubical form and look much more like an epithelial lining to the follicle. This marks the first appearance of the membrana granulosa. The cell bodies at this stage are small as compared with the nuclei, and are therefore very little in evidence. The particular follicles shown in the drawing are somewhat flattened, no doubt in preparation of the specimen. The ovum here measures $\cdot 045$ mm. long by $\cdot 025$ mm. broad. The ovum practically fills the follicle as in the dormant follicles. The nucleus is a little larger than that of a dormant ovum, and measures $\cdot 02$ mm. in diameter. There is no fibrous tunic yet developed, although here and there concentric fibres can be seen which look as if the fibrous tunic was beginning to form. The figure shows well how the flattened cells increase in number and size to form the membrana granulosa, three distinct stages being present in the drawing. These follicles are the

furthest away from the surface of the ovary; the deeper ones always appear to begin to mature first.

Fig. 3 marks an important stage in the maturation of the Graafian follicle. It shows a further proliferation of the now well-marked membrana granulosa, the formation of a zona pellucida (zona radiata) to the ovum, and the appearance of a well-marked fibrous tunic to the Graafian follicle. The membrana granulosa, mostly two-layered, consists of cubical cells whose bodies are still inconspicuous, and whose nuclei are elongated in a radial direction. The zona radiata of the ovum appears to be incompletely formed, and has on its outer surface small pointed projections which extend between the cells of the membrana granulosa. The ovum measures $\cdot 065$ mm. in diameter and the nucleus $\cdot 025$ mm. in diameter. The follicle is now obviously larger than the ovum, and measures $\cdot 115$ mm. in diameter. The fibrous tunic of the Graafian follicle appears to be forming, and is obviously a concentric arrangement of the ovarian stroma cells which surround the follicle. There are no obvious blood-vessels in the fibrous tunic.

Fig. 4 shows general enlargement of the follicle due to the great proliferation of the cells of the membrana granulosa. These cells have the same character as before, and here and there among them can be seen spaces filled with coagulated material which no doubt represent the commencement of the formation of liquor folliculi, apparently appearing at four or five places among the cells. The follicle now measures $\cdot 18$ mm. in diameter, the ovum has increased to $\cdot 075$ mm. in its longest diameter, and the nucleus remains at $\cdot 025$ mm. in diameter. The zona radiata is the same thickness all round, and shows similar pointed projections to those shown in the last figure. The fibrous tunic in this particular specimen is not very well marked.

Fig. 5 shows great enlargement of the follicle owing to the formation now of a large quantity of liquor folliculi, great proliferation of the membrana granulosa, and a well-marked discus proligerus. The cells of the membrana granulosa now have more obvious cell bodies. The follicle now measures $\cdot 39$ mm. long by $\cdot 33$ mm. broad, the ovum $\cdot 09 \times \cdot 075$ mm., and

the nucleus $.03 \times .025$ mm. The pointed projections on the zona radiata are still seen.

Fig. 6 shows still more enlargement of the follicle, the liquor folliculi being relatively greater in amount, the cells of the membrana granulosa proliferated still more and thinned out on the side away from the discus proligerus. The follicle now measures $.8 \times .7$ mm., the ovum $.1 \times .095$ mm., and the nucleus $.03$ mm. in diameter. This ovum apparently has reached the maximum size found in children's ovaries, at all events it is the maximum size found and measured in this series of specimens. As the mature human ovum from an adult is stated in text-books to measure about $.2$ mm., it would seem that the ovum in præ-menstrual life does not reach the same size as it does in adults; this no doubt might be expected. The cells of the membrana granulosa in this specimen have well-developed cell bodies. The fibrous tunic is well marked, but does not materially differ from the ovarian stroma around except that more blood-vessels are seen in it than are commonly seen in the ovarian stroma. This marks the commencement of that vascularity which will give rise later to a species of granulation tissue. This Graafian follicle may be taken on the average as the size of the mature follicle in præ-menstrual life, and at this point in general retrograde changes begin. However, at this stage it appears that there is often an excessive amount of liquor folliculi produced, giving rise to such an enormous enlargement that the size of 5 mm. in diameter or more may be reached. In these larger follicles no further development of the ovum is found, and the appearance of the ovum and discus proligerus remains the same, the only difference being that the membrana granulosa becomes more and more thinned out on the side away from the discus proligerus, and may be represented by a single layer of cells only. The proof that these very large follicles are physiological and not pathological has not been absolutely made out in this research, but it seems more than probable. These large follicles show the great vascularity of the fibrous layer, and sometimes show definite commencement of granulation tissue. The largest contracting follicle measured is shown in

Fig. 12, and measures 1.1 mm. in its longest diameter. It may be confidently supposed that contraction occurs very rapidly, and so this follicle must have been considerably larger than 1.1 mm. in diameter when at its greatest size before contraction began. In any case it must have been much larger than the mature follicle shown in Fig. 6. Not uncommonly retrograde changes begin in follicles smaller than that in Fig. 6. For instance, in Fig. 7 retrograde changes are obviously well advanced, because the ovum is being destroyed by phagocytic cells, and yet the follicle only measures .23 mm. in diameter. In some of the specimens even smaller follicles than this can be seen undergoing retrograde changes.

Retrograde changes.—These must be described, as they affect the ovum, the membrana granulosa, and the wall of the follicle. The ovum can generally be recognised in the contracting follicles if sufficient serial sections are cut. Fig. 7 shows the commencement of the invasion of the ovum by cells which appear to act as phagocytes. In this specimen the zona radiata is closely beset on one side by cells of the membrana granulosa, and appears to be thicker than usual. In disintegrating ova as a rule the zona radiata appears to be thicker than usual as if it were swollen by imbibition of some fluid substance. This is shown in Figs. 7, 8, and 9. In the ovum itself of Fig. 7 there are four cells to be seen which appear to have destroyed a part of the ovum itself, a lunated outline of the ovum abutting on these cells. The ovum is shrinking away from the zona radiata all round. The zona radiata appears to be the most resistant part of the ovum, for in most of the specimens observed it seems to be the last part of the ovum to be completely destroyed, and retains its staining powers a long time after the main body of the ovum is disintegrated. Fig. 8 shows a somewhat similar condition, but here the change has advanced further, as the interior of the ovum is entirely occupied by these invading cells, seven in number. The next section in series on this slide shows how these invading cells have got into the ovum. The zona radiata is deficient at one side, as if it had been broken down by these cells, and then, as it appears to be very resistant, more

cells have passed in through the same opening instead of destroying more of the zona radiata. In some specimens only the zona radiata can be seen, both the ovum and the invading cells apparently having disappeared. It may be argued, on the other hand, that these apparently phagocytic cells are not so in reality, but are simply granulosa cells which have been ingested by the ovum. This process has been shown to occur in some animals and is connected with the building up of the ovum rather than with retrograde changes. The present view is based largely on specimens 7, 8, and 9, and especially 7. The lunated outline of the ovum in No. 7 strongly suggests a hollowing-out process by these cells, and certainly seems opposed to the view that the cells are simply ingested, for in that case the ovum would be expected to increase in size—which is not the case here. Again, the phagocytic view is upheld by the large numbers of cells which seem to be passing into the ovum in specimens 7, 8, and 9 through a single opening in the zona radiata. The invading cells have uniformly similar characters wherever they are seen. They have spherical bodies .01 mm. in diameter on the average, their protoplasm is vacuolated as if they were swollen up with drops of fluid, and their nuclei are slightly oval and apparently absolutely identical with those of the cells of the membrana granulosa. The nuclei of these cells are generally displaced to one side as if crowded out by the vacuoles. The origin of these cells is a question of great physiological interest, because all the appearances point to their identity with the cells of the membrana granulosa. There are two possibilities with regard to their identity—they may be membrana granulosa cells or they may be leucocytes. With regard to the second possibility, these cells are quite unlike any of the usual forms of leucocytes, either the polynuclear, the lymphocytes, or the eosinophiles. The character of the nucleus is the chief determining point in this, because with regard to size of cell body there is not much difference. If these cells are leucocytes there should be some evidence in the sections of diapedesis as showing the origin of them from the capillary vessels; but a prolonged search has not shown a

single place where a leucocyte can be seen emerging from a vessel. On the other hand, the nuclei of these cells are identical in appearance with those of the cells of the membrana granulosa, and in many specimens these cells can be seen among those of the membrana granulosa, various sizes being present as if the essential change was simply one of swelling of the cell body from ingestion of fluids. From these considerations it appears that these cells really are identical with those of the membrana granulosa. There is no reason why the cells of the membrana granulosa should not take to themselves the properties of phagocytes; every recent research points to the fact that it is not only the white blood cells which exert phagocytic powers, but that others, such as the endothelial cells of blood-vessels, may have the same properties. All these cells owe their common origin to the mesoblast, and from our knowledge of the transmutation of epithelial cells it must be admitted that it is at least possible for the cells of the membrana granulosa to become phagocytes. In some follicles very large numbers of these cells are seen, all having the same characters; they cannot all take part in the destruction of the ovum, and it must be said that the functions exercised by these large numbers of cells are by no means clear. It may possibly be that they absorb some constituent of the liquor folliculi. The ultimate fate of these cells is clear in the sections. They undergo necrobiosis, the nuclei gradually lose their staining powers, the cell bodies lose their distinct outline, and eventually they break up and no doubt are absorbed by the granulation tissue of the fibrous layer of the follicle. All stages of disintegration of these cells can be seen in the sections. In some of the sections the ovum seems to undergo necrobiosis without invasion by the cells of the membrana granulosa, but as a rule one or two solitary cells can be seen in the ovum. The first method is without doubt the common one by which the ovum is got rid of.

The fate of the membrana granulosa will be partly gathered from what has been already said, but all its cells do not give rise to these swollen phagocytic cells. Many of the cells of this layer disintegrate without any further change, and fragmentation

of the nucleus, loss of staining properties, and general break up of the cell seems to be the fate of the majority. The first noticeable change in this layer as a whole is a shrinking away from the fibrous tunic of the follicle, thus losing its supply of nutriment. Then some of the cells become phagocytes, and others simply break up. In any case, before much contraction occurs in the follicle nearly all the cells of the membrana granulosa have disappeared.

The fibrous tunic of the Graafian follicle, which has been already shown to be but little marked in the earlier stages of development, later undergoes a well-marked series of changes which result in the formation of a kind of granulation tissue. The first change noted is increase of capillary blood-vessels in the fibrous coat, sometimes to a remarkable degree. This is well shown in Fig. 10, which is a drawing of a follicle measuring $1.2 \times .64$ mm., in which the membrana granulosa is shrinking away from the fibrous wall. Along with this increase in the vessels there is a proliferation of the connective tissue cells in the fibrous tunic, the whole producing a richly cellular, very vascular tissue extending equally all round the follicle. This layer is easily distinguished from the membrana granulosa by the presence of so many vessels in the former, while there are none in the latter. This layer rapidly increases in thickness and the blood-vessels form definite capillary loops such as one constantly associates with granulation tissue. Between the capillary loops the cells arrange themselves in a more or less radiating manner with their long axes at right angles to the wall of the follicle. This tissue is well shown in Fig. 9; the great thickness of this tissue and the fairly sharp line of demarcation between it and the ovarian stroma is obvious. At the same time what may be termed the "indifferent layer" develops on the surface of this tissue towards the follicle. Apparently this layer consists of coagulated lymph thrown out from the blood-vessels, and in it new connective tissue begins to form in the follicle. Fig. 9 is also interesting because it shows, in addition to the granulation tissue and contraction of the follicle, the ovum full of phagocytic cells, and the production of new fibrous tissue; all these changes going on at the same time.

Fig. 11 shows very well a portion of one of the capillary loops with the radiating cells and new connective tissue forming inside the "indifferent layer." The whole follicle at this stage is shown in Fig. 12, which is a drawing of a follicle measuring $1.12 \times .83$ mm. Here can be seen the granulation tissue, "indifferent layer," and new delicate connective tissue forming inside the follicle and gradually filling it up. The projection into the follicle is no doubt a spur of granulation tissue and ovarian stroma, apparently formed by a doubling in of the follicle wall, probably from pressure. In this particular follicle there seems to be nothing much left to absorb except some coagulated fluid left after the membrana granulosa has disintegrated. From this time the follicle fills with connective tissue, upon which the granulation tissue gradually encroaches, compressing it and possibly reabsorbing some of it, so that still later the follicle presents the appearance shown in Fig. 13. Here the granulation tissue can be still recognised in places, the "indifferent layer" can be seen, and the compressed scar tissue inside is obvious. Three large swollen cells can be seen in the drawing which are no doubt some phagocytic cells which have not yet disintegrated. The blood-vessels now are not so numerous; they have apparently done their work, and seem to have contracted from pressure of scar tissue.

The final result of the process is a small knot of scar tissue which can easily be recognised, but which is of variable size, possibly depending on the original size of the follicle at its maturity. In Fig. 13 the follicle only measures $.26 \times .21$ mm. Scars of this size can be seen in all children's ovaries, but when further contraction occurs there may be some difficulty in recognising these structures. Small corners cut off larger scars might easily appear as final results of cicatrisation, so that it is important to carefully examine serial sections before arriving at a decision with regard to the smallest scars. In general these scars leave no trace on the surface of the ovary, but it is not uncommon to find slight infolding of the surface. When this occurs it probably means that the follicle was much larger than usual before contraction began. The two sections of ovaries

shown in Fig. 14, which are drawn three times their natural size, could hardly be expected to show no infolding of the surface when such large follicles contracted. There is no doubt that when such large follicles are found the retrograde changes are postponed for some reason, and the large size is due to great development of liquor folliculi. Beyond this pouring out of fluid there is no evidence of a pathological change. In none of the seventy pairs of ovaries examined was there any evidence of an adenomatous transformation. A very large proportion of these ovaries contain follicles from 2—3 mm. in diameter, and from this frequent occurrence it cannot be supposed that they are in any way pathological, especially as many of them already show commencing granulation tissue in their walls preparatory to contraction and absorption.

It is interesting to speculate as to the reason for this series of changes in the ovaries of infants.

In the present state of our knowledge of the functions of the ovary we are forced to conclude that this organ plays a dual rôle, namely, that of supplying the female sexual cells and the production of some internal secretion which is essential to the well-being of the female up to a certain age. It is clear that the supply of sexual cells is unnecessary in infants, and so the follicles do not burst, but it is not certain at all that the internal secretion is unnecessary. In all probability this plays an important part in the development of the female child. It may be conceived that these constant changes in the Graafian follicles are in some way the source of this internal secretion. At present, however, we have no evidence to offer in favour of this, and it must remain but a most fascinating theory.

The drawings illustrating this paper have been made from different ovaries, irrespective of age; but it must be understood that all the changes described may often be seen in the same ovary, and the ovaries of a child of one year may show them just as well as those of an older child. The drawings have all been made with a Zeiss Camera Lucida.

CONCLUSIONS.

1. The Graafian follicles and ova in præ-menstrual life mature by a constant well-marked series of changes.
2. The ovum never reaches the same size as that of an adult female.
3. The size of the correspondingly mature Graafian follicle is variable, but usually measures about .8—1 mm. in diameter.
4. The ovum is removed by a kind of phagocytosis as a rule, but may undergo simple necrobiosis.
5. The phagocytic agents are the cells of the membrana granulosa.
6. The follicle eventually contracts by means of granulation tissue formed in its fibrous tunic, which eventually absorbs the remains of the membrana granulosa and liquor follicles.

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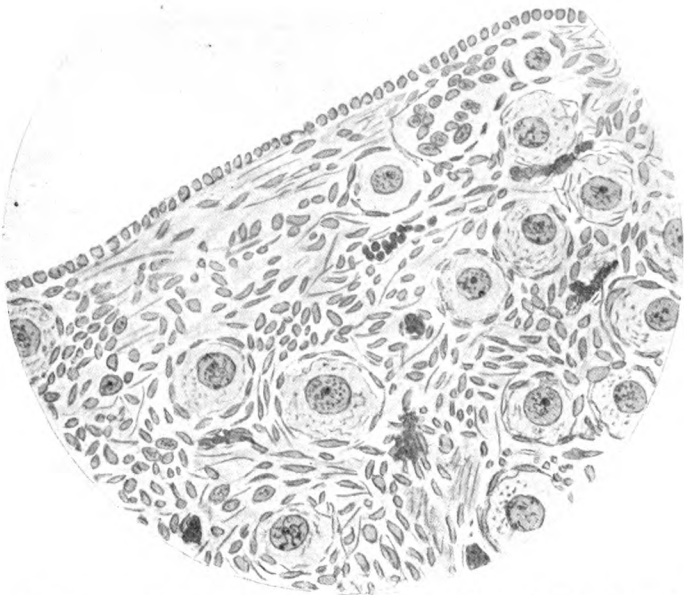


FIG. 1.—Young “dormant” ova. Average size $\cdot 0325$ mm. in diameter. $\times 300$.

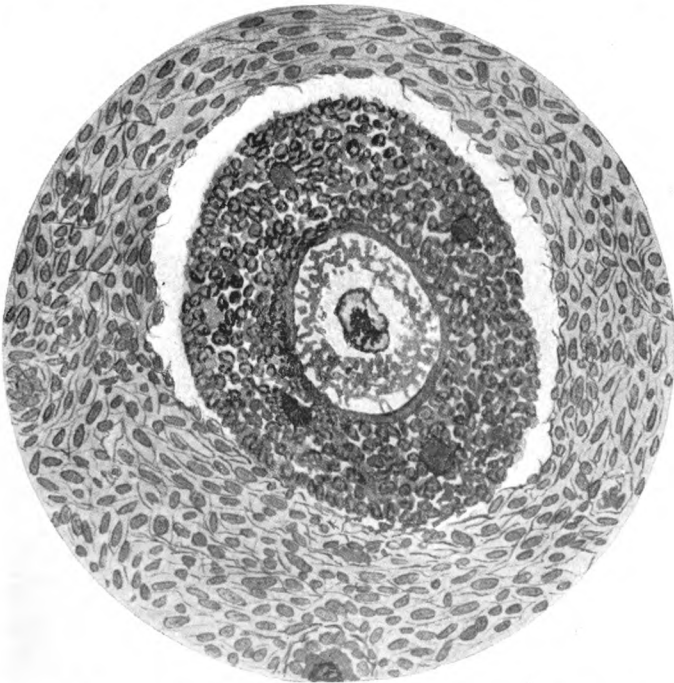


FIG. 4.—Enlarging Graafian Follicle. Membrana Granulosa many layered. Ovum measures $\cdot 075$ mm. in diameter. Follicle measures $\cdot 18$ mm. in diameter. $\times 220$.

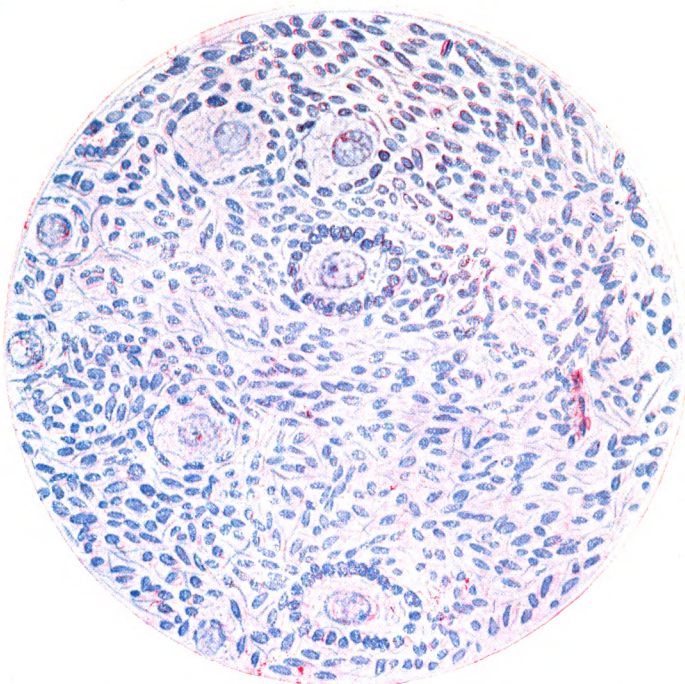


FIG. 2.—First changes in Graafian Follicle. Ovum measures $\cdot 045 \times \cdot 025$ mm. Three stages of growth shown. $\times 300$.

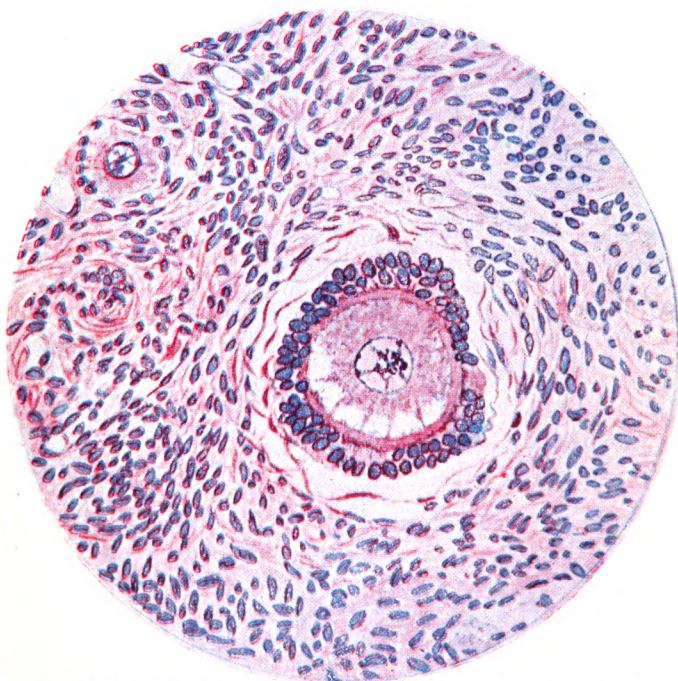


FIG. 3.—Enlarging Graafian Follicle. Membrana Granulosa two-layered. $\times 300$.
Ovum measures $\cdot 065$ mm. in diameter.
Graafian Follicle measures $\cdot 115$ mm. in diameter.

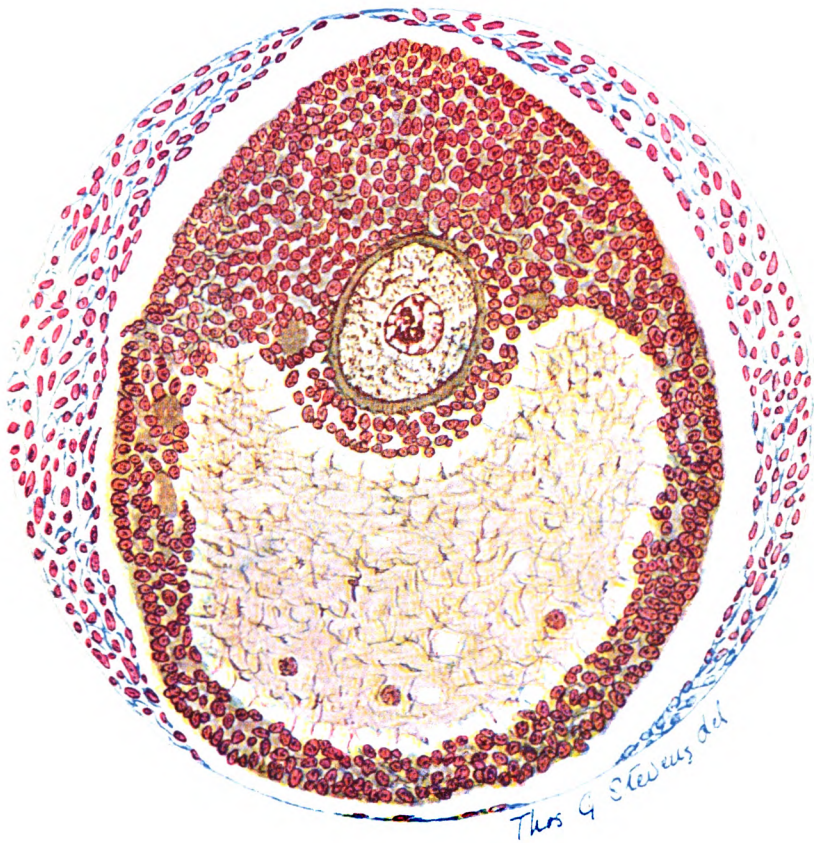


FIG. 5—Enlarging Graafian Follicle. Liquor Folliculi. Discus Proligerus. $\times 280$.

Ovum measures $\cdot 09 \times \cdot 075$ mm. in diameter.

Follicle measures $\cdot 39 \times \cdot 33$ mm. in diameter.

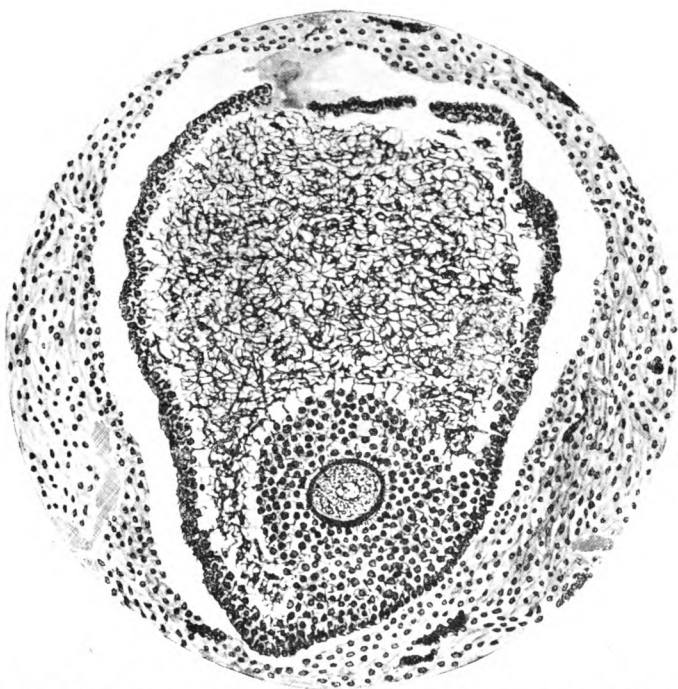


FIG. 6.—Fully-formed Graafian Follicle and Ovum. $\times 100$. Ovum measures $.1 \times .095\text{mm}$. Follicle measures $.8 \times .7\text{mm}$.

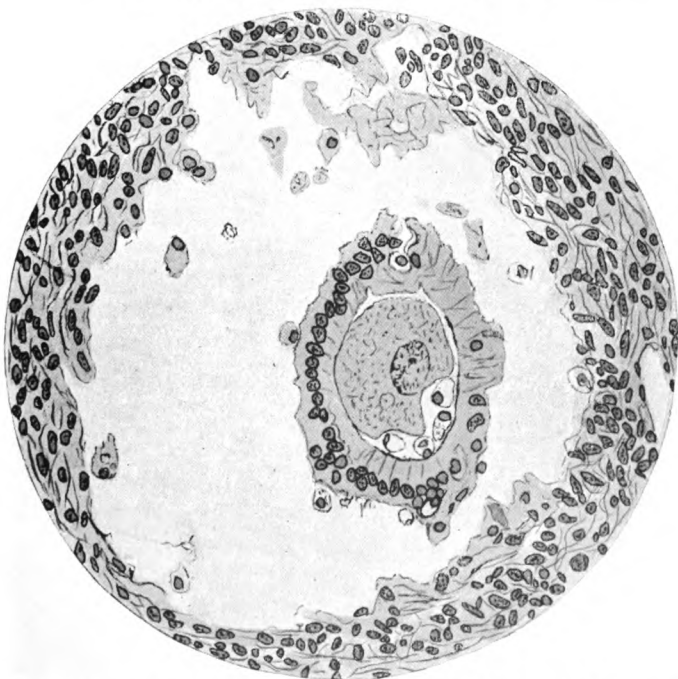


FIG. 7.—Retrograde change. Invasion of Ovum by Phagocytic Cells. $\times 310$. Disappearance of Membrana Granulosa. Follicle measures $.23\text{mm}$, in diameter.

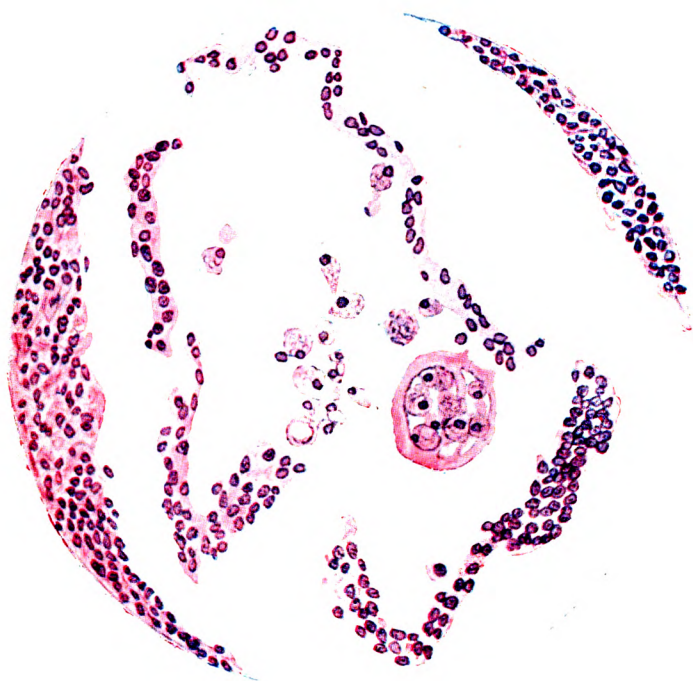


FIG. 8.—Retrograde changes. Invasion of Ovum by Phagocytic Cells. $\times 270$.
Membrana Granulosa breaking up.

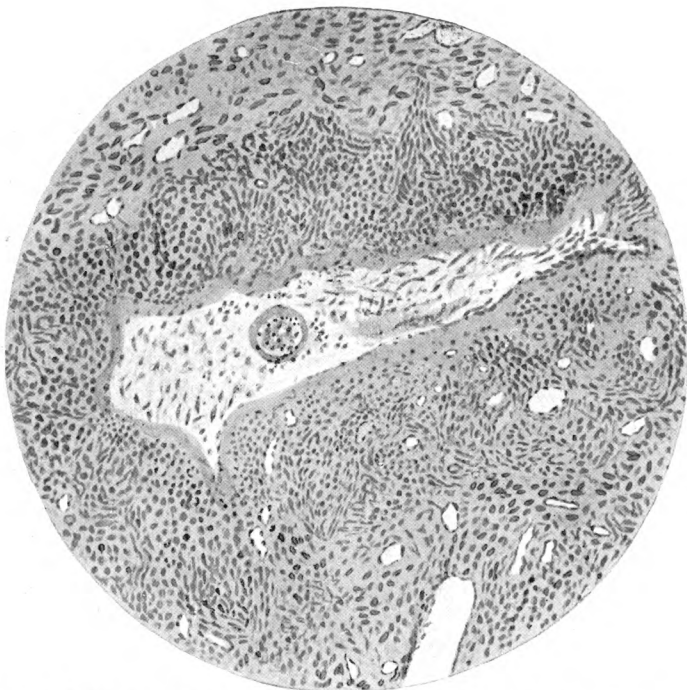


FIG. 9.—Retrograde changes. Ovum, phagocytic cells, contracting Graafian follicle, granulation tissue. $\times 73$.

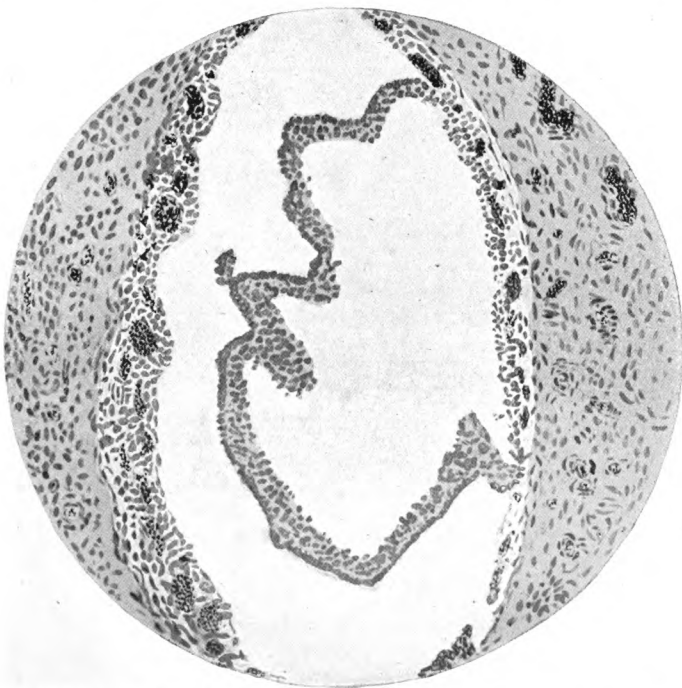


FIG. 10.—Retrograde changes. Commencing granulation tissue in fibrous tunic; very large blood vessels. $\times 75$.

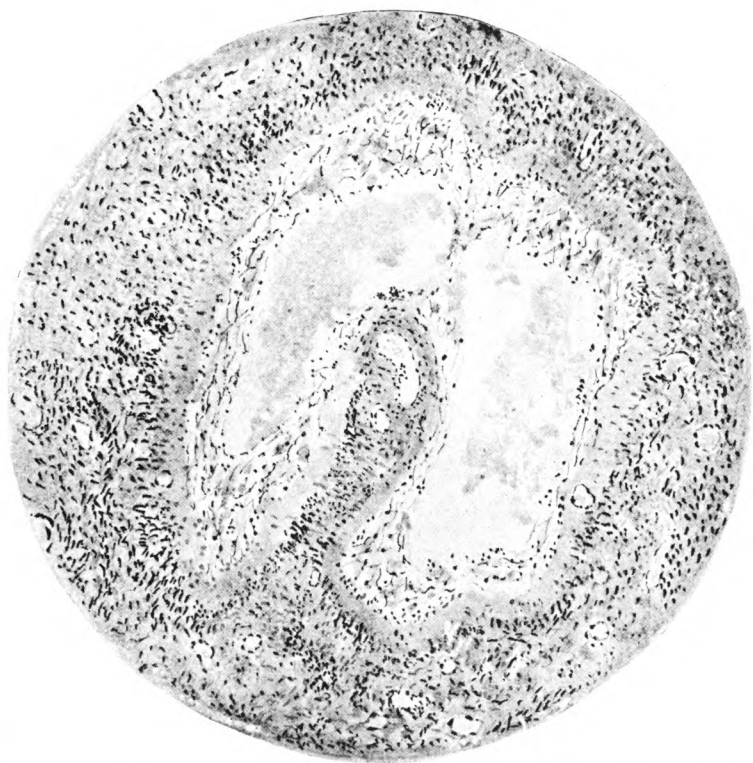


FIG. 12.—Retrograde changes, contracting follicle, granulation tissue, new fibrous tissue. Follicle measures 1.2mm. \times .64mm. \times 62.

THE PREVALENCE OF TRICHOCEPHALUS DISPAR.

By HERBERT FRENCH, M.D.,

AND

A. E. BOYCOTT, M.D.

From the Gordon Laboratory, Guy's Hospital.

No investigations seem to have been made in recent years as to the prevalence of intestinal worms among the general population in this country. The present results are derived from the microscopical examination of the stools of five hundred in-patients of Guy's Hospital. The cases were taken consecutively by beds all through the hospital, without any selection, over a period of ten months, and comprise surgical and medical as well as gynæcological and other special patients. Nearly all were inhabitants of London.

The method of examination was to shake up a small portion of the fæces with normal saline solution in a test-tube; after allowing the mixture to sediment for about half-an-hour the supernatant fluid is poured off and the deposit shaken up with fresh saline. This process is repeated four or five times, and by it all the finer *débris* is removed; one drop of the final deposit containing the eggs in a concentrated form is mounted fresh, and any eggs present are readily detected under a low power. The method is chiefly of value where very few eggs are present. In such cases eggs are often found where a negative result has been obtained in the direct examination of the unwashed fæces.

Unless the time allowed for sedimentation is unreasonably curtailed, there is no danger of eggs being lost during the washing. In more than four-fifths of the cases each sample was examined independently by two observers, the whole of the deposit under a seven-eighth of an inch square cover-glass being searched methodically on a mechanical stage.

Eggs of parasites were found in forty cases; in one *Ascaris* eggs were discovered with difficulty in a boy æt. 6, who had been admitted to the hospital as a case of *Ascaris* infection; in the remaining thirty-nine, eggs of *Trichocephalus dispar* were found. We did not meet with the eggs of any other parasite. The following table shows the details of these cases with regard to age distribution:—

Age.	Total cases examined.	Cases in which eggs were found.	Percentage infected.
0—5	42	1	2·4
5—10	43	5 (+1 <i>Ascaris</i>)	11·9
10—20	86	9	10·5
20—30	96	12	12·5
30—40	58	7	12·1
40—50	69	3	4·4
50—60	51	2	4·0
60—70	19	0	0
over 70	3	0	0
age not given	38	0	0
	500	39	7·8
		+ 1 <i>Ascaris</i> .	

These figures indicate a well-marked susceptible period of life; 84 per cent. of the infections fall between five and forty, while but 57 per cent. of the cases examined come within that age period. The absence of infections in children is striking; the single case in the period 0—5 years was aged four, so that in the first four years of life we have forty-one cases with no infections.¹

The sex incidence is equal: of 279 males 22 (=7·9 per cent.), and of 221 females 17 (=7·7 per cent.), were found to be infected.

¹The presence of *Oxyuris* is often missed by the ordinary methods of examination of fæces. We have had the opportunity of comparing in a number of cases the results of the microscopical examination of fæces with a subsequent microscopical search for the adult worms after the administration of thymol. In the former the eggs or worms were seen extremely seldom, while in the latter specimens of *Oxyuris* were nearly always found.

As might be expected, nothing suggestive is found in the diseases with which *Trichocephalus* was associated. Roughly speaking, 45 per cent. of the infected patients were medical, 30 per cent. surgical, 7 per cent. gynæcological, and 10 per cent. were suffering from affections of the eyes. Of twenty-four cases of appendicitis, two (8·3 per cent.) had worms; as this is rather less than the average incidence (9·4 per cent.) in all the cases of the same age period, no support is afforded to the notion that *Trichocephalus* has any ætiological relationship to appendicitis.² The length of time between the patient's admission to the hospital and the discovery of eggs varied from two to one hundred and three (average twenty-seven) days. In no case were the eggs numerous, and in the majority not more than one to three were found in a drop of the washed fæces.

The results have indeed no pathological interest; they indicate rather the extent to which the general population in London comes into contact with human fæces. The life-history of *Trichocephalus dispar* is not elucidated in all detail, but the essential facts seem to be fully established. The eggs measure about 55 by 25 μ , and as they leave the host in the stools contain an undifferentiated ovum; further development is very slow, and many months are occupied in the growth of the larva within the egg. This growth is to some extent independent of temperature, and will take place at "room-temperature" in this country. The thick egg-shell is very resistant; in consequence the embryo can survive great vicissitudes of temperature and moisture, and may remain capable of development for a long time (up to five years—Davaine) after leaving the body. The larva does not escape from the egg outside the body, but only on being taken into the alimentary canal. Eggs which do not contain a developed larva are not infective. As far as is known, infection can only take place *per os*. The length of life of the adult worm in the human intestine is, we believe, quite unknown; analogy would lead us to suppose that it may extend to several years.

Monkeys and lemurs are said to be often infected with *T. dispar*; in this country, however, this is of no moment in the present

² Metchnikoff, Bull. de l'Acad. de Méd., vol. xlv. 1901, p. 301.

connection. Closely allied, but distinct, species are found in several of the domestic animals—notably *T. crenatus* in the pig and *T. affinis* in the sheep. The eggs of these other species very closely resemble those of *T. dispar*, but the specificity of worm infections practically precludes the suggestion that the eggs which we have found in human stools are other than those of *T. dispar*, and that the infections with this worm had their origin in fæces other than human.³

It follows from this that infection arises by the ingestion of material contaminated with stale human fæces. Immediate personal infection or reinfection is excluded by the fact that the eggs must go through a lengthy period of development outside the body before they become infective. Any interest which our result may have lies in the demonstration—which is, we believe, unequivocal—that all the precautions which are taken in this country to secure the safe disposal of human excreta have not been adequate to prevent a purely fæcal infection being present in at least 8 per cent. of the population.⁴

On the other hand, it is satisfactory to note that these results indicate a far more efficient cleanliness than do similar statistics from other places, a selection of which follows:

Place.	Number examined.	Percentage with <i>Trichocephalus</i> .
Erlangen ⁵	1755	11.1
" (insane) ⁵	138	100
Dresden ⁶	1939	2.5
Kiel ⁶	1117	32.2
Dublin ⁶	90	90
Greenwich ⁶	16	69
Paris ⁷		50
Naples ⁷	80	100
Bâle ⁸	752	23.6
United States (insane) ⁹	500	10.8
Porto Rico ¹⁰	5490 (?)	6+
Cornish Miners ¹¹	48	79
India ¹²	1249	4.4
" ¹³	?	90

³ It is possible, though hardly credible, that the eggs found might have been the eggs of some other species of *Trichocephalus* which had been swallowed and passed through the body as such. In any case, the infection must be fæcal whether it be human or animal.

The cause and nature of the infection are such that, apart from variations in the method and thoroughness of the examination, the degree of infection must vary quantitatively with the degree of faecal contamination. This can be estimated directly only by an intimate knowledge of the details of the habits of the people concerned. The only instance which has come under our personal observation fully supports the connection: Cornish miners have hitherto worked in very filthy surroundings, and are infested with worms. Many of the statistics quoted refer to the experience of some thirty years ago, and it may well be that much improvement has taken place since then.

As far as our own cases are concerned, the paths of infection cannot be definitely traced; the absence of the worm in young children¹⁴ suggests somewhat strongly that infection is brought about by the ingestion of "ordinary" food, since in other ways children would appear to be particularly liable to take in undesirable material. Among the common articles of diet, the readiest mode of infection is offered by uncooked vegetables, and perhaps especially by water-cress, which is eaten very commonly by the poorer classes in London, and which is often derived from sources which are open to the gravest suspicion of sewage contamination. The greater part, at any rate, of the London water is subjected to some sedimentation before delivery; as the eggs settle very

⁴ It follows from the long duration of the infection that this figure is to some extent an accumulated result, and possibly also partly the result of conditions now past.

⁵ Leuckart, *Transl. Hoyle*, i. 1887, p. 151.

⁶ Cobbold, *Parasites*, 1879, p. 179.

⁷ C. Davaine, *Traité des Entozoaires*, 1877, p. 209.

⁸ Blanchard, *Traité de Zoologie Médicale*, 1889, i. p. 783.

⁹ Bull. no. 13, Hyg. Lab., U.S. Pub. Health and Mar.-Hosp. Serv., Washington, 1903; other statistics will be found here.

¹⁰ Report of Commission on "Anæmia" in Porto Rico, San Juan, 1904.

¹¹ *Journ. of Hygiene*, iv. 1904, p. 477; subsequent experience has fully confirmed this figure.

¹² Dobson, *Report on Ankylostomiasis*, 1892.

¹³ Hektoen and Riesman, *Pathology*, i. 1901, p. 344.

¹⁴ This point is brought out in the Erlangen statistics (children 4·8, adults 13·1 p.c.), but not in those from Kiel (children 32·5, adults 29·5 p.c.). Blanchard, *Traité de Zool. Méd.*, i.

Sex and Age.	Disease.	Differential leucocyte count: Percentages.					
		Lympho- cytes.	Inter- mediate.	Large hyaline.	Neutro- phile.	Eosino- phile.	Mast- cells. ¹⁵
M 36	aneurysm of aorta	9	15.5	19	55.5	1	0
M 39	chronic nephritis	27	21	6	42.5	2.5	1
M 31	crushed hand	21	19.5	3.5	53.5	1	1.5
M 12	mastoid disease	14	9	6.5	68.5	2	0
M 24	hip disease	14.5	11	6.5	63.5	4	0.5
M 25	acute rheumatism	21.2	20.2	3.2	51.6	3.8	0
M 25	detached retina	23.5	15.5	14.5	45.5	1	0
M 23	acute pericarditis	23.4	10.4	1.2	61.4	3.2	0.4
M 48	hemiplegia	28	11	2	56.5	1.5	1
M 28	mitral disease	31	12	3	53.5	0.5	0
M 16	sciatica	36.5	11	1.5	47	3.5	0.5
M 52	hemiplegia	23	17	2	56	2	0
M 7	empyema	12.5	5	1.5	80.5	0.5	0
M 20	detached retina	28	15	4.5	46.5	4.5	1.5
M 24	sight failure	25	16.5	8.5	49	1	0
(M 6	<i>Ascaris</i>	34	7.5	6	49	3.5	0)
F 38	phthisis	22	8	2	66.5	0.5	1
F 19	endometritis	20	6	2	70	1.5	0.5
F 40	?	5.5	6.5	1.5	86	0.5	0
F 23	chlorosis	20	13	4	57	5.5	0.5
F 8	pneumonia	32	9.5	3.5	53	2	0
F 19	acute rheumatism	31.5	6	2	59	1.5	0
F 35	lupus	36	6	4.5	49	3.5	1
F 9	hip disease	27.5	8.5	2.5	57.5	3	1
F 11	acute rheumatism	46	7.5	4	41.5	0.5	0.5
F 23	gastric ulcer	23.5	6	2.5	62.5	3.5	2
F 16	exophth. goitre	40	6.5	2	50	1.5	0

Av. 2.1

quickly, this would seem to exonerate the water supply, apart from the influence of filtration.¹⁶

The opportunity has been taken of investigating the condition of the eosinophile leucocytes in some of the cases. The above table of twenty-six cases confirms the opinion previously expressed¹⁷ that *Trichocephalus* infection, at any rate of the mild degree which was here present, is not accompanied by an eosinophilia.

We have much pleasure in acknowledging the invaluable help which has been rendered by our laboratory assistant, J. R. Clark, in obtaining these results, which, without such efficient aid, would have been long delayed.

¹⁵ Mast-cells were always present, though sometimes none were found amongst cells actually enumerated.

¹⁶ Cf. Blanchard, *Archives de Parasitologie*, III. 1900, p. 485.

¹⁷ *Journ. of Hygiene*, iv. 1904, p. 468.

CARCINOMA AND GASTRIC HYDROCHLORIC ACID.*

Thesis for Degree of M.D. Cambridge.

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At no period of the world's history has a more important subject than cancer occupied the field of scientific thought, and never has a larger body of skilled investigators been employed on a single line of research. The discovery of the exact cause of cancer—if such be possible—would confer on mankind incalculable benefits; and, as the avenues of approach to this problem are innumerable, there is plenty of material for the independent worker. There is every justification, then, for this paper which is devoted to the discussion of a small part of the problem, but a part which has hitherto received but scant attention.

Among all the facts which are known about carcinoma as occurring in various parts of the body, but few are capable of expression in figures; excepting, of course, statistics, arguments from which are so often fallacious, few of these known facts can be investigated on the lines of the exact sciences. Among these few there stands out prominently the postulate that free hydrochloric acid is absent from the gastric juice in nearly all cases of

* An abstract of this paper has appeared in *The Bio-Chemical Journal* Vol. I., Nos. 8 and 9.

† The expenses of this research were paid by Dr. Pembrey out of a grant from the Royal Society.

carcinoma ventriculi. This, then, indicates one direction in which the problem of cancer may be attacked and an effort made to decide whether that absence be due to some condition of the patient secondary to the presence of carcinoma in his body, which seems unlikely, or to the situation of the carcinoma in the stomach itself.

The first observations on HCl in carcinomatous stomachs were made in 1842 by Dr. Golding-Bird, of Guy's Hospital, and published by him in the *London Medical Gazette*¹ of that year. He estimated on three occasions at intervals of a week the vomit of a man, aged 44, who was found after death to have suffered from a dilated stomach which reached down to the pubes. The dilatation was due to a stenosed pylorus, which would hardly admit a fine probe—the stenosis being caused by a scirrhus mass the size of an orange, which was ulcerated in several places on its gastric aspect. Dr. Golding-Bird examined the vomit only, and estimated the acids by distillation and incineration of residue; this he boiled with dilute nitric acid and mixed with silver nitrate—the resulting silver salt being weighed. He concluded that in this case “Free hydrochloric exists in considerable quantity in the vomited fluids during the more irritative stages of the disease, and gradually disappears as the power of life sinks.” He also observed that the place of the hydrochloric acid was taken by organic acids, “probably lactic, acetic, and butyric.” To Ewald is due the credit for discovering this very early contribution to the pathological chemistry of the stomach, but it was an isolated observation and remained uncorroborated for thirty-seven years; moreover, the clinical value of the estimation is slight, though its chemical method is excellent, as only vomit was tested, and the estimated free HCl varied from 10·652 gr. on October 28th—“the more irritative stage”—to 1·0 gr. on November 17th of the same year, too rapid a change to be due to the carcinoma alone. Moreover, he seems to have attributed it to the gastric dilatation, and obtained similar results from a case of non-malignant stenosis.

The paramount influence of the dilatation on the presence of the HCl seems to have at first influenced the next observer, R. von den Velden, who comes after a long interval in 1879, as in his

first paper,² using methyl violet as an indicator, he found that free HCl was absent in each of the eight cases which he examined, though he subsequently extended the statement to include those cases in which dilatation was not present.

Stiénon³ examined eight cases also repeatedly, and found, on using Günzburg and methyl violet, that in four cases free HCl was always absent, while it was transitory in the remaining four. Rosenheim⁴ examined sixteen cases and was never able to demonstrate free HCl in fourteen of them on examining the gastric contents at the height of digestion. Both these observers published their results in 1888, and both concluded that in the majority of cases of carcinoma ventriculi free HCl is absent, though the fact of its presence would not carry great weight in the presence of undoubted clinical symptoms of the disease. These conclusions were verified by Boas,⁵ who could find no HCl in the gastric contents of fourteen cases, while in the fourteen cases examined by Honigmann and Von Noorden,⁶ who worked in Riegel's clinic, though free HCl was never entirely absent, it never existed in more than very small quantities.

All the investigators of the past eighteen years, since the publication of the results I have just quoted, have been unable to disprove the statement of Ewald that it is "substantially true that in most cases of carcinoma ventriculi no free hydrochloric acid is present," as some flaw can nearly always be found in the technique of those observers who have come to a different conclusion. Some have confounded organic acids with inorganic; while others, by estimating the chlorine, have included those inorganic salts which were ingested with the food.

Too much stress has, however, always been laid on the diagnostic importance of the mere presence or absence of free HCl, however small the amount may be. Günzberg's reagent is so very delicate that a percentage of free HCl, infinitely less than normal, will give a positive reaction, and a positive reaction so obtained would strengthen the case of those who deny the absence of free HCl in carcinoma ventriculi, though its very great diminution would be just as strong an argument for the other side. In other words, quantitative rather than qualitative experiments should

always be made, and no experiment accepted in which the percentage of free HCl has not been measured. If this were always done, probably every observer would agree that in *all* cases of cancer of the stomach, as soon as the earliest stages of the disease are passed, the free HCl *is considerably reduced in quantity*; and they would readily accept Franz Riegel's statement that "in carcinoma ventriculi *insufficient* secretion of HCl is the rule,"⁷ rather than Osler's more dogmatic remark, "that free HCl is absent in a large proportion of all cases of cancer of the stomach—84 out of 94 which were examined."⁸

One curious exception is noted to the almost universal diminution of free HCl in cases of carcinoma ventriculi—when carcinoma develops on the site of a previously-existing simple ulcer the hydrochloric acid secretion of the stomach continues normal up to death. Hemmeter has collected twenty-eight cases⁹ in which such a sequence took place without any diminution in the HCl, and Osler and McCrae corroborate him, but without giving statistics.¹⁰ Rosenheim says that 6 per cent. of cases of carcinoma ventriculi develop from simple ulcer, and that then the patient always maintains normal gastric secretion:¹¹ but such a statement is very hard to prove, and rests entirely on a history of gastric symptoms preceding the supposed commencement of the carcinoma. Moreover, the importance of the exception is considerably diminished by more recent researches, for Sir Cooper Perry and Dr. Shaw,¹² as a result of examining the post-mortem records of three hundred and six cases of carcinoma ventriculi, could find evidence of *associated* simple ulcer in only twelve cases, and in most of these there was no proof that the cancer had started in the ulcer, or had even occupied the same region of the stomach.

No satisfactory reason for the frequent absence of HCl has been given, and it is strange that more work has not been done with a view to its explanation. Golding-Bird and von den Velden considered that it was due to the dilatation which so often accompanies the resulting pyloric stenosis. Ewald¹³ gives the accompanying catarrhal inflammation or atrophy of the mucous membrane as the sole cause, and mentions three cases in which these conditions were absent, and HCl was secreted in copious

— —

quantities. Hammerschlag¹⁴ collected some cases in which the histological condition could be compared with the chemical findings, and stated that

1. If HCl was present there were no changes in the mucous membrane.
2. If HCl was absent, but lactic acid present, then the specific gland elements were absent and cylindrical epithelium or fibrous tissue substituted.

With the exception of these few investigations, the remaining writers on carcinoma ventriculi seem to have contented themselves with bare statements of possible explanations; but few seem to have considered the possibility that the absence of HCl may be due to the carcinoma *per se*, and these few dismiss it scornfully in a few words. Thus Ewald, "Carcinoma in itself as an histological new growth has nothing to do with the diminished HCl—it is not caused by any mystic influence of cancer."¹⁵ And again, Franz Riegel in Nothnagel's Practice, "When I began my investigations I was inclined to the opinion that carcinoma itself, or possibly certain products that the neoplasm generated, inhibited the HCl of the stomach. This view has since been shown to be erroneous." Neither of these statements is supported by any statistics or descriptions of observations, and the only experiment I can find, with the exception of Professor Moore's experiments, is in Sidney Martin's "Diseases of the Stomach," where he says that he has once observed by means of a gastrostomy that the HCl was present in normal quantities in a case of cancer of the œsophagus.

Professor Moore, with Messrs. Alexander, Kelly and Roaf,¹⁶ examined the gastric contents of seventeen cases of cancer in various situations, to find out how the presence of cancer in the body affected the gastric secretions; they made the startling discovery that in nearly all cases of cancer—wherever its seat—the gastric hydrochloric acid is absent, or greatly reduced. This, so far as I can find, is the only effort that has been made to prove so close a connection between malignant disease and the stomach. I have worked on the same lines in examining my cases, and have shown in my deductions how far our results agree.

As I have also examined several cases in the surgical wards in whom there was no evidence of malignant disease, it is important to consider those cases in which—apart from carcinoma ventriculi—free HCl is absent from the gastric contents. Sidney Martin divides the conditions in which diminished secretion of HCl occurs into three classes.¹⁷

1. Long irregularities of diet, either in amount, quality or accessories.
2. Definite anatomical changes in the gastric mucous membrane, such as atrophy of the glands or catarrh.
3. Influences which exist in the body outside the stomach and affect the stomach either through its blood or nerve supply.

The first two classes are easy to understand, but it is the third class which has the most important bearing on this paper. Long lists are given in various text-books of the conditions in which free HCl may be absent—but the inclusion of most of these conditions in the list rests on very slender evidence, often on single instances. Sometimes the vomit alone is relied on, with no reference to the period of digestion; and nearly always the colour test has alone been used: the list has been copied from text-book to text-book, and but rarely investigated with any scientific accuracy.

1. Anæmia is generally mentioned as a cause of reduced HCl, and is probable, though no extensive or accurate observations have been made. So far as I can find, chlorosis has never been investigated in this way, though it is the commonest form of anæmia. In “anæmia with chronic dyspepsia,” Leube¹⁸ found great deficiencies in three cases. Pernicious anæmia is mentioned in the list, but I can find no literature on the subject. The severe anæmia which accompanies atrophy of the stomach has probably been mistaken for Addison’s “idiopathic” form, and so the mistake has been perpetuated.

2. All infective fevers are said to cause diminution in HCl secretion, and the evidence appears to be that Manassein,¹⁹ working with animals, which he rendered

febrile by injecting putrid material into the veins, found that their gastric juice possessed no digestive properties unless HCl were added.

In three cases of typhoid fever, Cahn and Von Mering²⁰ found the percentage of free HCl was .058, .006, .00 respectively, and the only other work I can find is that by Wolfram and Gluzinski.²¹ The former examined fifteen cases of pyrexia, of which only five were infectious, and the latter three, two of which were infectious. Typhoid and typhus, so far as I can find, are the only infectious fevers which have been investigated.

3. Tuberculosis has been extensively investigated, especially phthisis, and the recorded observations vary considerably. Klemperer²² found no diminution in the secretory activity of the stomach. O. Brieger²³ made three hundred experiments on sixty-four cases of phthisis, and found that the free HCl varied from .05 to .19 per cent., while the diminution was greater in the worst cases, but bore no relation to the fever. Hildebrand's²⁴ results are, however, probably more correct, as he used Günzburg and methyl violet, and found free HCl always present in non-febrile cases, but absent during pyrexial stages in febrile cases.

Dyspepsia is often a prominent symptom in phthisis, though it is strange that in many patients the appetite is enormous and the digestive capabilities very great.

4. Malaria is mentioned, but the only evidence seems to be that Leube²⁵ found severe dyspepsia in two cases.

5. Addison's disease is quoted on the authority of Kohler.²⁶

6. Bright's Disease (Rosenthal).²⁷

7. Diabetes is given, but I can find no evidence.

8. Catarrhal Jaundice. Hemmeter²⁸ made one hundred and eighteen analyses of the vomit in twenty cases, and found free HCl always absent in sixteen of them.

9. Tabes has been given.

10. Gastric Neuroses sometimes manifest themselves by absence of HCl in the gastric secretion, or even by entire absence of all secretion.

11. According to Krehl,²⁹ carcinoma situated anywhere in the abdominal cavity may inhibit the secretion of HCl in the stomach. This observation, which is not supported by any reference to cases or statistics, is in accordance with Moore's views, and is an isolated statement so far as I can discover.

METHODS OF ESTIMATING FREE HYDROCHLORIC ACID IN GASTRIC CONTENTS.

In order to be able to judge correctly of the different methods of estimation it is of the greatest importance to make quite clear what is meant by "free" hydrochloric acid, as it is by assigning different meanings to this word "free" that such large discrepancies occur between the findings of various observers in this field.

When Bidder and Schmidt³⁰ first demonstrated HCl as the active acid in the gastric secretion they worked on pure gastric juice unmixed with food, and described the acid so found as "free," which it undoubtedly was; but their immediate successors in analysing gastric contents discussed as "free" acid all that was *not* combined with the inorganic bases to form salts, entirely forgetting that some of the acid so described was combined with proteids, and so was not entirely free. The freedom depends, in the case of each molecule of acid, on the strength of its attachment to the complex proteid molecule, and also on the dissociating strength of the reagent with which it is brought into contact: and at the same time they forgot—or rather did not yet know—that other organic acids are present in the gastric contents of abnormal stomachs, all of which they had included in their term "free."

Later, that part of the hydrochloric acid which enjoyed sufficient freedom to be able to attach itself to reagents, such as tropæolin or Günzburg's reagent, came to be called "free"; while the word "combined" was applied to the hydrochloric acid which, while

attached to the organic substances present, still retained the ordinary activities of acids, and could reveal itself to the chemist by uniting with ordinary alkalies in the presence of litmus or phenolphthalein. Those molecules of HCl which had united with inorganic bases to form salts had now ceased to be recognised as acids.

It is impossible to determine the degree of attachment of all the various hydrochloric acid ions which are in combination with the organic substances present in the gastric contents some time after a meal containing any proteid. So the attention of the writer of this paper is confined to the acid which is present in sufficient freedom to carry out a certain well-known chemical inversion.

The usual method employed in estimating the free HCl in the gastric contents is that recommended by Mintz, in which a given quantity of filtered gastric contents is titrated against a decinormal solution of NaOH, until it no longer responds to Günzburg's test. Thus the alkaline solution is run in a little at a time, and between each addition a few drops are removed from the gastric contents which are being estimated, and these drops, together with some Günzburg's fluid, are evaporated to dryness on a water bath. If the characteristic pink colour appears, free HCl is still present unneutralised, and some more alkali must be run in until the reaction can be no longer obtained. There are, however, several objections to this method.

These estimations are generally carried out with small quantities of gastric contents, and the removal of even a few drops, if often repeated, lessens the amount of acid present and requiring neutralization. Thus, as the test has often to be repeated five or six times, and occupies, therefore, unless the observer be very expert, a period of thirty minutes before the reaction disappears, the figures obtained thereby would be slightly too low. Also, if organic acids be present some of the alkali used will go towards neutralizing them, even though no indicator be present to show how far towards neutrality those acids have advanced.

The other objections apply to Günsburg's fluid as a reagent; if a positive reaction be obtained it is certain that free hydrochloric acid is present; but we may fail to obtain this result when gastric juice contains albumin, peptone or salts in considerable quantity, *even if free HCl be present also*.⁸¹ Mierzynski⁸² considered also that the fluid often reacted to acid phosphates—so that many factors affect the reliability of estimations obtained by Mintz's method.

The latest and best method of estimating the acids of the gastric contents depends on a determination of the concentration of the hydrogen ions in the solution, which concentration is proportional to its inverting power. It is a matter of common experience that different acids have different strengths; equi-molecular solutions of two such different acids as acetic and nitric require the same amount of a certain solution of sodium hydrate to neutralise them, though their acid properties are very different. We should describe the nitric acid as "much stronger" than the acetic, so that in measuring the effective acidity of any given solution the ordinary methods of titration entirely fail.

Na_2CO_3 in solution is more or less dissociated into Na_2 and CO_3 , the degree and ratio of dissociation depending on the dilution. The CO_3 ions combine partly with the H ions to form HCO_3 , and the corresponding OH ions produce the alkaline reaction. If now by addition of a little acid a few of the HO ions are removed, the equilibrium is disturbed, and a new quantity of Na_2CO_3 is dissociated; a process which is repeated every time a new quantity of acid is added until all the carbonate is dissociated. The dissociation of the carbonate existing in the original solution, upon which the number of OH ions is dependent, cannot therefore be determined by titration; and in the same way the dissociation of an acid in solution cannot be exactly determined by titration.

Now hydrochloric acid, in concentrations such as are found in gastric contents, is over 95 per cent. dissociated into its ions, and has correspondingly greater effective acidity than the organic acids which occasionally occur in the stomach, and in similar concentrations are only dissociated to about 3 per cent. Thus,

in estimating the effective acidity of any solution of gastric contents, it is the hydrochloric acid, not the organic acids, which really determine the result, as the latter can be neglected.

In 1889, F. A. Hoffman pointed out this method of determining the free acid in gastric contents, and published some results on the suggestion of W. A. Ostwald.⁸⁸ The catalytic power of an acid—or the velocity at which it can hydrolyse any substance capable of hydrolysis—is directly proportional to the concentration of its hydrogen ions; the former can be accurately measured, and hence the latter can be accurately deduced.

As Hoffmann originally described the experiment, he employed cane sugar solution as the hydrolysable substance, and I used the same substance for some time in my initial experiments, but found that I was unable to attain any high degree of accuracy. The amount of inversion of a solution of cane sugar of known strength produced by a certain amount of the gastric contents is measured by a polarimeter, readings being taken before and after incubation, at a given temperature. I found that the yellow colour of the gastric contents prevented the passage of the polarised light, and that any effort to decolourise the solution altered the percentage of acid. Charcoal, for instance, which is a favourite decolourising agent, takes up large amounts of free acid from any solution passed through it.

Professor Moore, however, in his research used methyl acetate, and this I have found to be a much better reagent for measuring the catalytic power of the various solutions. Methyl acetate, in the presence of an acid, is changed into methyl alcohol and acetic acid, and, if a constant solution of methyl acetate be used, the velocity of this conversion is proportional to the concentration of the hydrogen ions present in the solution. The period of action is known, and the quantity of acetic acid produced is the difference between titration after and before the action, so that the velocity and therefore the concentration can be calculated. The acids contained in the gastric contents—hydrochloric, &c.—are unaltered by the catalysis, so that they appear equally in both titrations, and accordingly disappear on taking the difference between the two.

The velocity of reaction at any instant is proportional to the molecular concentration at that instant of the substance undergoing change. Now, if A be the molecular concentration at the beginning of the reaction, and x the amount of dissociation which has taken place at the end of the time t , then $\frac{dx}{dt}$ is the expression for the velocity of reaction at any instant. Using these signs the above can be expressed mathematically as

$$\frac{dx}{dt} = C (A - x) \text{ where } C \text{ is a constant}$$

$$\text{or on integration } C = \frac{1}{t} \log \frac{A}{A-x}$$

Where A is proportional to the amount of acetic acid into which it is possible to convert a given quantity of methyl acetate, and so can be estimated by allowing quantities of methyl acetate and $\frac{N}{10}$ HCl to incubate until titration of 5 c.c. with normal soda gives a constant result. Thus, 40 c.c. $\frac{N}{10}$ HCl and 2 c.c. of methyl acetate were incubated at 37° C; at the beginning of incubation 5 c.c. were equivalent to 4.9 c.c. soda, after forty-eight hours to 28.8 c.c., and after seventy-two hours to 28.7 c.c. Thus A is proportional to 28.8—4.9, *i.e.*, 23.9. Similarly, x is proportional to the amount of acetic acid that has been produced in the time t , or to the difference between the initial and final titration—before and after incubation.

Since we are always concerned with the *ratio* of A to $A-x$, we may dispense with the “proportional to” and take A and $A-x$ as actually representing these quantities. Also the above equation, being obtained by integrating a differential equation, requires that the logarithms used in its expression should be Napierian and not Common; but the latter are easier to work with, as they are given in all mathematical tables; and, as they always bear a fixed ratio to the corresponding Napierian, I have used common logarithms throughout, and the numbers in the column giving the various values of C should be all multiplied by 2.3026. This is, however, unnecessary, as the numbers in the last column representing the percentages are always obtained from the *ratio* of two numbers out of the preceding column, and, as this factor always vanishes, the last column represents the true percentages.

THE ROUTINE OF EXAMINATION.

Before the patient was given a test meal he fasted for 14 hours, as by this means it was ensured that the stomach was empty; unless, indeed, its motility was very much impaired, an unlikely event, as the patients examined complained of no gastric symptoms. A light supper, consisting of bread and butter, and milk or soup, was given at 6 p.m., and nothing more was allowed till 8 a.m. the following day, when the patient was given a pint of weak tea with a few drachms of milk and a little sugar, together with a large slice of buttered toast. This differs from the ordinary test meal given by Ewald in containing more proteid, as he gave no sugar, milk or butter. As my purpose was to estimate the active hydrochloric acid in the gastric juice, and, as Pawlow has demonstrated that plain bread produces a much smaller flow of gastric juice than does proteid, in order to conduct the experiment under more advantageous conditions, I considered it advisable to introduce some proteid into the meal.

If, however, organic bases be present in considerable quantity in the gastric contents, they combine with the hydrochloric acid, which is accordingly prevented from responding to the tests for free acid; thus the figures obtained from a meal rich in proteids would be too low, even if the stomach were capable of secreting a normal quantity of hydrochloric acid. Another of Pawlow's discoveries also influenced me in the choice of a test meal. He proved that gastric secretion varies directly with appetite, as was demonstrated by his well-known experiment of "feeding" a dog by suggestion. Now, a more unappetising diet than dry bread and milkless tea cannot possibly be imagined, but the addition of butter and milk increased the patients' appetites, and so, therefore, the gastric secretion.

Many observers recommend lavage of the stomach before the test meal is given, but it is almost impossible to empty the stomach completely after lavage, and the residual fluid, which varies in amount, dilutes the subsequent gastric juice.

After an interval of an hour and a quarter to an hour and a half the stomach tube was passed, and some of the gastric contents syphoned off. In the majority of cases, the mere act of

passing the tube was sufficient to cause a gastric contraction, thus setting up a syphon action which, once started, continued for about a minute. Various methods have been devised for removing the products of digestion, most of which are quite unnecessary. Some clinicians use elaborate aspirators, which, however, Leube and Wiesner²⁴ consider dangerous, as injury may be done to the stomach by tearing off pieces of mucous membrane. Ewald used "the method of expression," in which the patient by straining, or the observer by pressing on the patient's abdomen, forced the contents of the stomach up the tube. The most recent invention is American; a double-channelled tube is passed down the œsophagus, and compressed air, driven in through one of the channels, enlarges the stomach and sends the products of digestion up the other channel. I have found, however, that when once the syphon action is established no further trouble is incurred; but, if necessary, a Higginson syringe, with a glass tube fitted into the receiver, can be applied for a few minutes and gently worked until the gastric contents begin to flow in the tube, when the syringe should at once be detached.

The fluid so obtained generally contained but little mucus, and the solid contents were usually finely divided. They were filtered through ash-free filter paper, the ash of ordinary filter paper being capable of taking up some of the free HCl. For example, 20 c.c. of a solution of HCl were passed through an ash-free paper when it was found that 5 c.c. required $3\cdot59 \frac{N}{100}$ NaOH to neutralise; on the experiment being repeated with an ordinary filter paper, 5 c.c. required only $3\cdot41 \frac{N}{100}$ NaOH; thus, for every 5 c.c. passed through it, the ordinary filter paper absorbed $\cdot18$ c.c. $\frac{N}{100}$ more than the ash-free paper.

Twenty c.c. of the filtered contents were then taken in a corked Erlenmeyer flask, and 1 c.c. of methyl-acetate added; 5 c.c. of the mixture were titrated with $\frac{N}{100}$ NaOH, free from carbonate, phenol phthalein being used as the indicator, and the results expressed in $\frac{N}{10}$ NaOH. As the fluid was yellow or brownish in colour, some difficulty was experienced in judging the exact point of neutralisation; so control solutions were used

for comparison in each titration ; and, as sufficient fluid was not always obtained to provide these controls, the fluid had occasionally to be diluted exactly before estimation, and the results multiplied accordingly. In the table the figures given for titration in Cases 5, 6, 8, 15, are those actually obtained ; and the values of C in the next column, the values for the original solution, are obtained by multiplying the figures accordingly.

The corked flask was then placed in a thermostat, which was maintained at a temperature of 37° C. ; but the temperature is quite immaterial, so far as the resulting figures are concerned, provided all the estimations are performed with the thermostat at the same temperature ; as the value of C for $\frac{N}{10}$ HCl is obtained in the same way. Moore⁸⁸ used a temperature of 45°, and Hoffmann used higher temperatures still ; but the higher the temperature the greater the evaporation. Moreover, it is probable that at higher temperatures some of the HCl in combination with proteid is dissociated therefrom, and goes to swell the total free HCl. After incubation for an interval which varied from five to six hours, according to convenience, the flask was removed, and 5 c.c. again titrated with the same precautions as before ; the difference between the two titrations was observed, and its value x gives the number of free hydrogen ions in the fluid according to the equation—

$$C = \frac{1}{t} \log \frac{A}{A-x}$$

TABLE OF RESULTS.

	Sex.	Age.	Disease.	Period of Digestion in Hours.	Titration with decit-normal Soda and Phenolphthalein.			Period of Incubation = t.	Constant of Velocity of Reaction 1/8°C.	Effective Acidity in HCl percentage.
					Initial.	Final.	Diffence = x.			
1	M	56	Epithelioma linguae	1½	3.3	9.54	6.24	5½	39.820	.1218810
2	M	56	Epithelioma linguae	1½	.53	.653	.123	5	.7469	.0023861
3	F	46	Carcinoma of colon	1½	2.31	3.237	.927	5½	5.2061	.0159348
4	M	61	Carcinoma recti...	1½	2.188	2.397	.209	6	1.0596	.0032432
5	F	43	Carcinoma mammae	1½	.85	.90	.05	4½	.744*	.0022772
6	M	66	Epithelioma of lip	1½	.053	.124	.071	5	2.1535†	.0065914
7	F	62	Carcinoma mammae	1½	.941	1.038	.097	5½	.5195	.0015901
8	M	48	Epithelioma floor of mouth	1½	.57	1.507	.937	5	28.9490†	.0886070
9	M	64	Carcinoma of oesophagus	1	.44	.44	.00	5	.0000	.0000000
10	M	62	Epithelioma penis	1½	.194	.33	.136	5	.82613	.0025286
11	M	63	Epithelioma floor of mouth	1½	2.012	2.026	.014	5	.0848	.0002595
12	M	57	Epithelioma linguae	1½	1.68	1.77	.09	5	.5462	.0016781
13	M	59	Epithelioma penis	1½	1.643	1.694	.051	6	.25769	.0007887
14	M	57	Melanotic sarcoma	1½	2.702	6.118	3.416	6	18.6091	.0569583
15	M	33	Pyonephrosis	1½	.254	.288	.034	4½	1.0847†	.0035201
16	M	44	Simple stricture of rectum	1	.91	3.29	2.38	5½	13.8050	.0422543
17	F	29	Chronic mastitis	1½	.60	.66	.06	5	.3639	.0011188
18	M	48	Conjunctivitis and keratitis	1½	3.17	4.8	1.63	6	8.5216	.0260830
19	M	29	F. W. M. P.	1	2.19	7.39	5.2	5½	32.2898	.0998300
20	M	28	A. S. M. P.	1	2.16	7.09	4.93	5½	30.40321	.0930572
21	M	28	T. W.	1½	2.39	6.69	4.3	6	23.9283	.0792390
			N HCl	—	—	—	—	—	119.2543	.0887007
			10	—	—	—	—	—	average	.365

* The value of 10°C. here given is twice that obtained from preceding columns, as contents were diluted twice.

† " " " " " five times.

DISCUSSION OF THE RESULTS.

1. Of the thirteen cases of non-gastric carcinoma which were examined only two showed normal gastric acidity. They were—a case of epithelioma linguæ, in which it was above normal; and a case of epithelioma of the floor of the mouth, in which it was almost exactly normal—normal being taken as equivalent to the mean of observations taken on three healthy young men.

2. Of the remaining eleven cases, one showed one-sixth the normal effective acidity; while the rest were all below one-fourteenth, most were below one-fortieth, several were below one hundredth of normal. Thus in the majority of the cases examined, the effective acidity was very greatly reduced, almost as much as in cases of carcinoma ventriculi. I suspect, indeed, that, if a similar series of cases of carcinoma ventriculi were examined by the same method, the results would be almost identical.

This would point to the conclusion that the diminution of HCl in cancer of the stomach is due to the presence of carcinoma in the body, and not to the position of the carcinoma in the stomach itself. And so far as my results go they uphold the views of Moore and his colleagues, although exceptional cases occur. It is interesting to notice that in his series of ten cases,* which he investigated by this method, a case of cancer of the tongue gave the highest percentage, .01239, though some of our lowest results also came from cases of tongue and floor of mouth.

3. It is well known that psychical influences play a great part in gastric secretion. Appetite, in the case of Pawlow's dog, increased the secretion of HCl; and a worried man is so often a dyspeptic, that I thought for some time that in this condition lay the solution of the low results which Moore and I obtained. I thought that the dread of approaching operation, or the horror of cancer always present in the lay mind, might cause the diminution. But in case 8, although the man was extremely worried and

* They have since published another series of cases with similar results.

harassed, his free HCl was normal; while in case 10 the free HCl was one-fortieth of normal, and yet never was there a happier patient or one more free from dread. Psychical influences alone do not seem to be the cause of the diminished secretion.

4. It is interesting to discuss the stage at which carcinoma affects the gastric secretion; and the evidence of my results shows that this change is not necessarily delayed till the later stages of the disease. Only four of my cases could be described as inoperable, 1, 3, 4, 11; and yet in case 1 the free HCl was *more than normal*, and in case 3, though much less than normal, yet it was the third highest value obtained. On the other hand, case 5, which gave one of the smallest estimations, exhibited a very small growth.

5. In only one case could cachexia be said to be apparent, and that was a case of cesophageal stricture—case 9—the gastric secretion from which contained no free HCl. The majority of the patients were healthy, so far as one could judge from external appearances; so that obvious cachexia cannot be the direct cause of the diminution.

6. The only case of sarcoma which I examined was one of melanotic sarcoma—probably the most malignant form of sarcoma; and yet it showed nearly normal free HCl, very much more than was found in eleven out of the thirteen cases of carcinoma.

7. I also examined four patients who were suffering from various non-malignant surgical affections, and in two of them I obtained very low readings, as low as most of the malignant cases; the other two were also less than normal. These cases are not sufficient in number to justify definite statements, but they certainly impair the value of the investigation of stomach contents as an aid to diagnosis; and suggest that the diet and life in a surgical ward lead to some diminution in the gastric secretion.

8. The almost complete absence of any symptoms of dyspepsia in all my cases was very striking: a phenomenon which Ewald explains by supposing a substitution of intestinal for gastric secretion.

I am much indebted to the Surgeons of Guy's Hospital for their kind permission to utilise their patients for the purpose of this investigation.

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CASES.

1. Thomas H., *æt.* 56.—A large inoperable epithelioma involving both sides of the tongue. Irritation from a tooth had been noticed for six months, but the tumour only two months. Much glandular enlargement, but no cachexia or wasting; he looked healthy and had no dyspepsia.

2. William M., *æt.* 56.—A small epithelioma on anterior part of tongue which was easily removed. Six weeks' history. Some glandular enlargement. No dyspepsia. Does not think he has lost weight.

3. Hannah C., *æt.* 46.—Carcinoma of hepatic flexure of colon involving peritoneum, which it had been found impossible to remove on laparotomy a few weeks before her stomach contents were examined. She said she had wasted and become paler. Slight dyspepsia.

4. William H., *æt.* 61.—Large definite carcinoma of rectum, for which a colotomy was subsequently performed. History of only three months' symptoms, and yet radical treatment was impossible.

5. Leah L., *æt.* 43. A small carcinoma of breast without much glandular enlargement. Only five months' history. She looked very healthy, and was not at all wasted. Slight dyspepsia.

6. Thomas G., *æt.* 66.—A small epithelioma of lower lip, which had started as a pimple seven months before. There were some glands which were found to be inflammatory, and the man was healthy and well nourished.

7. Hester N., *æt.* 62.—A small carcinoma of the left breast giving a few small glands. Twelve months' history. Not wasted.

8. Alfred E., *æt.* 48.—Extensive epithelioma involving floor of mouth, lower jaw, and submaxillary glands. He was wasted, though there was only a four months' history, and very worried and nervous about his operation which was going to take place on the morrow.

9. Charles B., *æt.* 64.—An oesophageal stricture which was considered to be malignant—the bougie passing about twelve inches. Swallowing had been painful for about six weeks, and he was very wasted.

10. Henry M., *æt.* 62.—A very large growth at end of penis, which had been growing for twelve months. There was no loss of weight and no cachexia. This man was particularly cheerful—assured me that it was not "cancer," and that no operation was necessary.

11. William W., *æt.* 63.—Large epithelioma which involved most of the right side of the floor of his mouth, and caused much difficulty in swallowing. Only two months' history, and yet it was inoperable.

12. Job T., *æt.* 57.—Fairly large epithelioma of the tongue, with a history of two months. There was no wasting, and he was a healthy-looking man. Operation refused.

13. Edwin B., *æt.* 59.—A very large foul epithelioma at end of penis which had been growing for six months. There was no cachexia, but he had lost half a stone in six months. His general condition was good in spite of the growth, and he denied all symptoms of dyspepsia.

14. Charles B., *æt.* 57. A large melanotic sarcoma which had started growing from a mole on abdominal wall near umbilicus twelve months before, and had already given secondary deposits in the axilla. The man was very fit, not at all wasted and had no dyspepsia.

15. Walter S., æt. 33. A large pyonephrosis on the right side, which had produced hæmaturia for four months, and frequency of micturition for two months. The kidney was thought to be malignant, but operation proved it to be a simple pyonephrosis, probably tuberculous. The man was very healthy in appearance and general condition—appetite good, no dyspepsia, no wasting, and a good colour.

16. Richard W., æt. 44.—A simple stricture of the rectum, which had given symptoms for thirteen years. He was slightly dyspeptic, and said he had lost twenty-three pounds in six months.

17. Emily F., æt. 29.—A case of mastitis following prolonged lactation. The tumour had suppurated and produced several indolent sinuses. Patient was very well, fat, and denied all dyspepsia. After scraping, the breast healed up very well.

18.—Richard G. S., æt. 48.—A case of conjunctivitis and keratitis with corneal ulcers.

19, 20, 21.—Healthy young men leading active lives.

In the above cases the diagnosis was usually made by microscopical sections of the growth; but in those cases where it was not possible to examine the growth histologically, the surgeon's diagnosis has been given.

NOTES ON THE EXAMINATION OF THE BLOOD.

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1.—SOME METHODS OF ESTIMATING HÆMOGLOBIN.

EVEN when large quantities of blood are available, it is not possible to separate the hæmoglobin quantitatively and proceed along ordinary chemical lines. Still less is it feasible to follow any such method when blood is only obtainable in those small quantities which are available in nearly all clinical and in many experimental investigations. It follows that the methods in use are all more or less indirect. Some are more indirect than others. Thus the calculation of the hæmoglobin content of blood from the specific gravity is highly indirect, while the method which depends upon the estimation of the iron may be said to be more nearly direct, in so far as a somewhat specialised property of hæmoglobin is under examination. Both these methods are of course altogether fallacious. The former depends on the assumption that the ratio between the specific gravity and the hæmoglobin is a constant. This may be nearly true for normal blood, but does not hold in many pathological conditions. The iron method requires that the percentage of iron in hæmoglobin is a known constant, and that either there is no iron in blood other than that in the hæmoglobin, or that the ratio $\frac{\text{total iron}}{\text{iron in Hb}}$

is constant. It is at least doubtful whether any of these requirements are fulfilled in fact. At best, these two methods must be described as clumsy and difficult procedures, whereby a very uncertain result is obtained. In themselves, and in conjunction with accurate hæmoglobin estimations, they give results of the highest value, but the interest lies largely in the variation of those ratios which are assumed to be invariable when the methods are used for ascertaining the hæmoglobin content.

Direct estimations of the oxygen capacity of blood are readily made, especially by the ferricyanide method of Haldane, but to obtain accurate results the quantity of blood necessary is considerable. The apparatus introduced by Barcroft and Haldane requires only 1 c.c. of blood, but seems to be difficult to manage satisfactorily. The ferricyanide is also imperfect when applied to human blood. The deduction of absolute amounts of hæmoglobin from the results obtained is rendered uncertain by the lack of very sure information as to the quantitative relations of hæmoglobin to oxygen.

The remaining prominent property of hæmoglobin—namely, its colour—is that on which depend practically all methods which lay claim to possessing the requisite combination of accuracy and practical utility. If a standard is at hand, the colour of which corresponds to that of a solution containing a known percentage of hæmoglobin, it is a simple matter to dilute a solution of unknown strength until a colour match is obtained; or if a number of standards, or a variable standard, are prepared, that which corresponds in colour with the unknown solution or sample of blood is easily selected. There is no doubt that these colour matches can be made with the greatest degree of accuracy, and all the hæmoglobinometers in common use are constructed on this plan.

The accuracy of any method which involves this colour-matching depends on (1) the accuracy of the standard, and (2) on the details of the procedure whereby the estimation is made. The principles which underlie this latter matter are relatively simple and easily fulfilled. A great deal of attention has been paid to their elaboration, while the far more difficult matter of the

accuracy of the standard to which the blood is to be compared has been to a large extent neglected. It is, however, clear that, in the absence of a correct standard, the ingenuity and mechanical skill which have been expended on such instruments as those of Fleischl-Miescher or of Dare are altogether wasted.

We may now discuss shortly some of the principles of construction and use which form the basis of a proper system of hæmoglobinometry.

(a) Nearly all methods involve the dilution of the blood. To avoid an error here requires merely accurate graduation of instruments. This is commonly adequately done by the makers, but it is always well to check the measurements.

(b) The standard may be single, variable, or multiple, as in the Gowers, Fleischl, or Oliver instruments respectively. As a matter of convenience and economy in construction it is clearly best to have a single standard, which also reduces the risk of inaccurate standardisation, and renders verification and correction much more simple. By constantly reducing the variable solution (blood) to the same standard, greater rapidity and precision are attained in matching any other colour to that standard. It also follows from the Weber-Fechner law that equal differences of intensity of tint will be the more obvious the less the intensities which are under comparison. The difference, for instance, between bloods containing 90 and 95 per cent. Hb respectively may not be perceptible; if, however, these same specimens are diluted a hundred times, the difference in tint is readily appreciated. Hence the standard should be pale.

(c) The pigment of the standard ought to be the same as that of the blood under comparison, *i.e.*, it should be hæmoglobin or some compound or derivative of hæmoglobin. The use of, *e.g.*, picrocarmine or coloured glass is bad, since the absorption of light in different parts of the spectrum by these pigments is not the same as that of hæmoglobin; hence the accuracy of the comparison depends on the illumination under which the estimation is made. This may be easily demonstrated by examining a sample of blood with a Gowers or a Fleischl apparatus, first by daylight and then by artificial light; the two readings will be quite different. The

inconvenience of being restricted to one particular method of illumination requires no emphasis. It is also difficult to imitate artificially the change from red to yellow which hæmoglobin solutions show on progressive dilution. Other pigments do not show the same change, and a red solution which is a perfect match with undiluted blood will in all probability entirely fail to correspond when both are diluted to one half.

(*d*) It is of obvious importance that the standard should be accurately constructed to correspond in colour with a solution of hæmoglobin of known strength. How this standardisation of the standard is done is not very often discussed, but it would appear that it is most commonly effected by comparison with a known solution of separated hæmoglobin or with the tint of the blood of adult males in whom nothing abnormal can be detected. The difficulties of the preparation of pure unaltered¹ hæmoglobin are such that the second method is not necessarily the less accurate. There is, however, no difficulty in the manufacture of standard which is accurate in terms of oxygen capacity. That this is precisely equivalent to content in hæmoglobin is not allowed by everyone, but since the oxygen capacity of blood varies with the colour, and it is hardly possible that the hæmoglobin can fail to vary with the colour, it follows that the oxygen capacity must vary with the hæmoglobin. It is, however, at present impossible to say definitely how much hæmoglobin corresponds to how much oxygen-capacity, so that such a standard must be constructed on the basis of an "agreed normal."

Many of the better-known hæmoglobinometers fail to comply with one or more of the conditions which have been laid down. The instruments of Fleischl (with the improved Miescher pattern), Dare and Oliver have a variable standard made of coloured glass, so that all are adapted for use in but one kind of light and are inadmissible. The Gowers instrument has a single standard; this, however, is made of picrocarmine, and is therefore bad. The

¹The change which is most likely to occur during the separation is the production of some methæmoglobin. The yellow of this is so different from the red of hæmoglobin as to render such mixtures wholly unsuitable for hæmoglobinometry.

modifications of this instrument introduced by Haldane² and by Sahli combine the advantages of the single dilute standard with the use of hæmoglobin pigment. It being quite impossible to preserve unchanged solutions of hæmoglobin, Hoppe Seyler tried the combination of CO with hæmoglobin, but found that it was liable to decompose. Haldane, however, showed that no change took place if the solution of CO-hæmoglobin is sealed up in an atmosphere of CO (or coal gas) and all traces of oxygen excluded. Such a solution forms the standard of the Haldane-Gowers instrument; it is standardised in terms of oxygen capacity. The great disadvantage of this pattern is that a supply of CO or coal gas is necessary to make an estimation. In the Sahli form, a solution of acid-hæmatin forms the standard, the blood under examination being diluted with 0.5 per cent. HCl. Theoretically this is the more perfect instrument, since there is no difficulty in carrying the necessary acid. The standard is, however, made to correspond with a 1 per cent. solution of "normal blood" in a somewhat indefinite way, and it seems to be very far from fulfilling the author's claim of permanency.³ These difficulties are, however, avoided if a Sahli standard is, from time to time, standardised against a Haldane standard, the latter being, if thought necessary, compared directly with fresh blood of known oxygen capacity. The desired association of accuracy and practical convenience is in this way secured.

The most recent recruit to attract much attention seems to be the instrument of Dare;⁴ on that account it deserves, perhaps, more extended notice. The blood is examined in a thin film undiluted; this avoids one source of error and is a great saving of time, an estimation, indeed, taking not more than a minute from first to last. The standard is a circular wedge of coloured glass. A standard candle illumination is necessary in a dusk or dark place. It possesses then at least two fundamental faults. The manufacture of the standard was conducted with the greatest care, as can

² *Journal of Physiology*, vol. xxvi., 1901, p. 497.

³ The only one which I have had an opportunity of examining had evidently faded very much, since it gave a result 35 to 40 per cent. too high.

⁴ *Philadelphia Medical Journal*, vol. vi., 1900, p. 557.

be judged from Dr. Dare's narrative: "To fix the 100 mark—the colour shade of normal blood—hæmoglobin prepared especially for the purpose by Messrs. Armour & Co., of Chicago, was reduced, and the impurity determined. The standard for normal blood was fixed at 13·77 grams. of hæmoglobin (adjustment being made for impurity) mixed with 100 c.c. of saline solution."⁵ The addition of 100 c.c. of watery liquid to 13·77 grams. of hæmoglobin gives a solution of a strength which is unknown to those who are not acquainted with the solution volume of hæmoglobin; it may perhaps be assumed to be about 12 per cent. No reason is given why such a low value should be taken as the normal, nor is any account given of the "impurity" in the hæmoglobin or of its estimation. The description, indeed, lends an air of altogether spurious precision to what would seem to have been but a vague process, just as the "additional marks" on the Miescher measuring pipette help to cover up the manifold faults of what is a beautiful piece of machinery, but a very indifferent hæmoglobinometer.⁶

By the kindness of Mr. Hawksley, I have been able to compare several of these hæmoglobinometers. The experiments given below were all made with one sample of sheep's blood. Five dilutions in saline were made of a strength unknown to the observer. After estimations had been made by the other methods, the samples were examined by a Haldane-Gowers instrument; the results of this last corresponded with those calculated from the dilutions. As the standard of the undiluted blood, the mean of five concordant observations with the Haldane instrument was taken as correct.

⁵ In the pamphlet accompanying the instrument, "serum" is substituted for saline.

⁶ It may not be out of place to remind readers that the relative cost of the Fleischl-Miescher, Dare, Oliver, Fleischl, and Haldane-Gowers instruments is about 126 : 94 : 84 : 73 : 31.

Dilution.	Calculated from dilution.	Haldane-Gowers. Mean.	Dare. Mean.	Miescher-Fleischl Mean.			Gowers 1	Gowers 2	Gowers 3 (flat tubes).
				Observ. X.	Observ. Y.	Mean.			
A		98·6	79·6	95·8	88·6	91·5	98	76	103
B	49·3	50	42·6	39·6	43·6	41·6			
C	65·7	63·5	56·5	54·8	51·2	53·0	62	54	67
D	82·1	80·5	83·0	71·2	77·2	74·2			
E	16·4	16	9·0	10·0	11·2	10·6	18	16	15
F	32·9	32·5	27·7	23·0	24·4	23·7	32	32	30

Additional accuracy is secured—so it is claimed—in the Fleischl-Miescher instrument by the provision of two chambers for comparison; the more shallow chamber should give readings $\frac{4}{5}$ of those obtained in the deeper. The following results were obtained as to this point:—

	Deeper Chamber Mean.	$\frac{4}{5}$	Shallow Chamber.			Haldane-Gowers.
			Observ. X.	Observ. Y.	Mean.	
A	91·5	73·2	44·0	56·8	50·4	98·6
B	41·6	33·3	23·0	26·2	24·6	49·3
C	53·0	42·4	34·0	32·8	33·4	65·7
D	74·2	59·4	46·6	48·0	47·3	82·1
E	10·6	8·5	6·1	6·0	6·0	16·4
F	23·7	18·9	14·8	15·2	15·0	32·9

The smaller chamber, then, gives readings a good deal less than $\frac{4}{5}$ those obtained with the larger chamber; in the majority of cases they are about half the true reading.

These observations are all the mean of five measurements. In both the Dare and the Fleischl-Miescher instrument one cannot see what reading is being obtained as the observation is being made. The variation among individual observations may be very large.

	DARE.					FLEISCHL-MIESCHER.									
A	86	65	77	89	81 = 79·6	101	90	90	97	101	=	95·8			
						94	91	88	84	86	=	88·6			
B	40	39	43	44	47 = 42·6	41	39	40	38	40	=	39·6			
						42	44	44	43	45	=	43·6			
C	57	55	56·5	63	51 = 56·5	56	55	55	56	52	=	54·8			
						55	50	52	50	49	=	51·2			
D	102	64	87	76	86·5 = 83·0	73	70	75	69	69	=	71·2			
						80	76	78	75	77	=	77·2			
E	9	8	8	10	10 = 9·0	12	10	10	9	9	=	10·0			
						13	11	11	10	11	=	11·2			
F	28	27	27·5	27	29 = 27·7	25	24	24	22	20	=	23·3			
						24	25	24	26	23	=	24·4			

The wide variation is seen especially with the more concentrated mixtures; this illustrates the difficulty of the upper end of the variable scale.⁷

It had been intended to make a parallel series of measurements with Oliver's tintometer method; it was, however, found impossible to obtain a proper match of colour, and no satisfactory end points could be obtained. The colour book of Talquist is not a hæmoglobinometer.

Summary.

A satisfactory colour hæmoglobinometer must be so constructed that:—

- (a) The colour match is made in highly diluted solutions.
- (b) The standard is composed of the same pigment as the unknown solution.
- (c) The standard represents some definite quantity.
- (d) The standard is permanent or capable of ready and repeated calibration.
- (e) The instruments which most nearly satisfy these conditions are the modifications of Gower's apparatus introduced by Haldane and by Sahli; the latter is simpler, but the standard does not appear to be permanent.

2.—THE DETERMINATION OF THE "ALKALINITY" OF WHOLE BLOOD.

The colour of blood renders the measurement of the alkalinity extremely difficult. At the same time the narrow variations which occur under both physiological and pathological conditions render necessary a high degree of accuracy. The fact that the blood is a very complex proteid solution, the reaction of which depends on acid and alkaline salts, makes the measurement of

⁷ It may be said that no particular accuracy is necessary at the upper end of the scale. This is far from being the case; for the most important diagnostic help—to say nothing of experimental work—may be obtained from the observation that an elderly gentleman has only 80 per cent. hæmoglobin. The Fleischl instrument and the Gowers picrocarmine standard in a faded state are probably responsible for the erroneous idea that 70–80 per cent. Hb is found in healthy people.

reaction more than usually dependent on the indicator used. The addition of foreign indicators is undesirable, and Dare⁸ has recently suggested that use should be made of an indicator which exists in blood already, *i.e.*, the hæmoglobin. In this method, 15 cub. m.m. of blood are diluted with $\frac{N}{400}$ tartaric acid and watched carefully with a spectroscope. He finds that the absorption bands of oxyhæmoglobin, CO-hæmoglobin, and methæmoglobin disappear "at the exact point of neutralisation." It is easy to satisfy oneself that this remarkable phenomenon is at least inconstant in occurrence. At room temperature, the oxyhæmoglobin and other bands are readily seen when highly diluted blood has been rendered strongly acid to litmus by the addition of tartaric acid. If, however, the temperature is somewhat raised and the time of reaction prolonged, a very obvious naked-eye change takes place. If to a series of small test tubes, each containing 20 cub. m.m. of blood and distilled water to a constant volume, $\frac{1}{800}$ tartaric acid is added in increasing quantities, and the tubes placed for ten minutes in a water bath at about 50° C., a sharp change in colour from red to yellow is noticed at some point. Spectroscopically it is found that the tube which has had most acid added and still remains red shows the bands of oxyhæmoglobin, while the next highest tube, which is yellowish-brown, shows no absorption bands. This "disappearance" of the bands is due to the fact that the derivative of hæmoglobin⁹ which is formed has much weaker absorption bands than oxyhæmoglobin, and in a corresponding strength these are often invisible. One may, however, be able to see traces of a band in the red. The tubes highest in the series (*i.e.*, most acid) which are still red, show a further change in that they have become opalescent, and on standing a white flocculent precipitate settles.

We have, then, two end-points; firstly, the production of a neutralisation precipitate of proteid, and secondly, the conversion of the oxyhæmoglobin into methæmoglobin (?). These end-points

⁸ Philadelphia Medical Journal, vol. xi., 1903, p. 137.

⁹ This is generally supposed to be methæmoglobin, and is certainly not easy to distinguish from that substance. There is, however, some doubt in the matter (Ham and Bailean Journal of Physiology, vol. xxxii., 1905, p. 314).

are very sharp, being as a rule quite distinctly present and absent in mixtures containing 20 c.c.m. of blood in a total volume of 2 c.c., and differing from one another by 0.1 c.c. of $\frac{1}{500}$ tartaric acid.

I have not been able to determine satisfactorily what relation these end-points bear to the reaction towards ordinary indicators (litmus, etc.). The method is thus only useful in a comparative way. It seems, however, to be more delicate, and is certainly more easy, than the usual procedures.

3.—THE DIFFERENTIAL LEUCOCYTE COUNT OF NORMAL PERSONS.

The value of a leucocyte count in diagnosis is well established. In many cases it is inconvenient, often altogether impracticable, to make an enumeration of the total leucocytes. Such an enumeration, if not made soon after the blood is drawn, is apt to be worse than useless, inasmuch as inaccurate and therefore misleading results are obtained. A dried film may, however, be prepared under any circumstances, and the examination postponed till a convenient time. A differential leucocyte count made on such a film may give most useful information, not only as to the presence of such "blood diseases" as leukæmia, but as to the existence of an ordinary neutrophile leucocytosis. Such leucocytoses, though seldom quite pure, are due to an increase of neutrophile cells, and are, therefore, demonstrated in the dried film by an increase in the percentage of neutrophiles. For a proper appreciation of the significance of such a count, it is necessary to know the proportion of neutrophiles which are normally present. Figures recently obtained differ widely from the older estimates which are in common use. The following are derived from counts of 500 leucocytes in dried films obtained from one hundred and fifty-four working adult men, who complained of, and obviously suffered from, no material illness. They are all from miners in different parts of England, and the great majority from underground workers, but there is no reason to suppose that this has any influence on the differential leucocyte count. Coal, tin, lead, zinc, and arsenic mines are included, and all give the same results.

The average figures are given in the next table. These receive confirmation from a series of counts which were made at the same time on miners infected with *Ankylostoma*. The latter showed an average eosinophilia of 18·2 per cent., and after deduction of the excess ($18\cdot2 - 2\cdot5 = 15\cdot7$) of eosinophiles, the counts are much the same as those for completely normal men. As far as I am aware, but one set of figures for the normal differential count of healthy English males has been published;¹⁰ these figures show a somewhat remarkable correspondence with those which I have obtained.

	No. of cases.	Lym- ph'c'tes	Inter- ¹¹ mediate	Large hyaline.	Neutro- phile.	Eosino- phile.	Mast- cells.
Normal miners	154	26·1	12·0	2·1	56·6	2·5	0·7
Miners infected with <i>Anky- lostoma</i> : corrected ...	148	25·2	9·4	3·5	58·5	2·5	0·9
Phear	49	44·4			54	1·9	0·7

The range of variation is also important. For neutrophiles Phear gives 45 to 60 per cent. The cases here dealt with are distributed as follows:—

35-	40-	45-	50-	55-	60-	65-	70-	75-	80-85 per cent.
5	10	15	31	40	29	19	1	2	2 = 154

Thus in 93 per cent. of the cases the neutrophiles lie between 40 and 70 per cent., and in 65 per cent. between 50 and 65 per cent.

Corresponding figures for the eosinophiles are:—

<1	1-	2-	3-	4-	5-	6-	7-	8-9 per cent.
29	48	32	23	10	5	5	1	1 = 154

¹⁰ A. G. Phear, Med. Chir. Trans., vol. lxxxii., 1899, p. 331.

¹¹ The classification of the non-granular cells is somewhat different from the usual one. "Lymphocytes" and "large hyalines" include only the cells which are quite typical of those classes; all other non-granular cells are placed as "intermediates." Most of these are cells which have relatively more cytoplasm than lymphocytes, and relatively less than large hyalines. They include also such cells as the (very uncommon) "large lymphocyte" *sensu restricto*, and form a mixed and heterogeneous group about which we know nothing.

And for the mast-cells:—¹²

<0·5	0·5	1·0	1·5	>2·0 per cent.
55	58	39	3	4

The normal percentage of neutrophiles was placed by Ehrlich at 70–72 per cent., and this figure is often quoted. It is, however, clear, as far as English blood is concerned at any rate, this figure is far too high. Recent French observers have found 60 and 66 per cent.¹³ As a rule a percentage of more than 70 indicates a neutrophile leucocytosis, and in three of the five cases of this kind in the present series I find that a note was made that there appeared to be a considerable leucocytosis.

¹² Mast-cells are always present in normal blood. The idea that they are often absent arose from the use of Ehrlich's triacid stain, in which the characteristic granules remain unstained instead of forming one of the most prominent features of a film stained with Jenners or one of the similar stains now in use. In ten of the above cases none were met with in the 500 cells counted, but a further search soon revealed them.

¹³ Bezançon and Labbé, *Traité d'Hématologie*, 1904, p. 487.

VACCINES AS AN AID TO SURGERY AND MEDICINE.

By MAURICE G. LOUISSON, M.B., B.S.

SURGEONS and physicians alike are now commencing to realise that in the case of a bacterial disease a patient may derive great benefit from the administration of a corresponding vaccine—a method of treatment due to the investigations of Sir Almroth Wright.

Wright and Douglas have shown that blood fluids perform a definite and independent rôle in connection with phagocytosis, and they arrived at this conclusion by testing the serum and the blood-cells separately. They showed the existence and presence in the serum of a substance which they called the opsonin—deriving this new term from the Greek word *ὀπσωνεω*, I cater for; and enunciated the doctrine that the more opsonin, for a particular organism, that is present in the serum, the greater will be the patient's resistance towards that organism. Bullock and Western have recently shown that there is more than one opsonic substance—that is to say, that opsonins are specific for the different bacteria on which they exert their opsonic action.

The treatment of bacterial infection by Wright's method consists in provoking an increase in the antibacterial substances of the blood by injecting into the patient an appropriate number of dead bacteria of the same species as that responsible for the morbid process. Expressed in Wright's own words, "We do not, in the case of these inoculations, supply to the patient protective

substances produced in the organism of an animal vicariously inoculated, but we induce the chemical machinery of the patient to elaborate by its own efforts the protective secretion which is required for the destruction of the invading bacteria. The elaboration of this protective secretion proceeds in accordance with the general law, that a vaccine introduced into the organism will, given that it is introduced in appropriate doses and at proper intervals, call forth a production of the specific bacteriotropic substances which are required for the destruction of the bacteria against which protection is desired."

So of that particular strain of organism which has acclimatised itself to grow in the patient's body, a fresh inoculation is needed, and the patient is cured by material obtained directly from the infecting virus—a remarkable fact, but true; hence it must be remembered that a vaccine differs fundamentally from an antitoxin. The meaning of the term "vaccine" has altered very considerably from its original use, and in the twentieth century Wright defines it as "any chemical substance which, when introduced into the body, causes there an elaboration of protective substances."

So much has been written of late on tuberculin and opsonic indices that I do not intend either to discuss tuberculous cases or detail the methods of estimating the amount of specific opsonins present in the blood, or indeed, so far as concerns the opsonic index, to do more than touch upon its uses; but propose in the following notes to confine myself to considerations based upon cases of bacterial infections—other than tuberculous—that have been treated by vaccine during the past year in Guy's Hospital.

As a result of this work, two points of great practical importance have been established—the first, that in the treatment of patients by vaccines (except in those cases necessitating the use of tuberculin) very good results can be obtained by attention to clinical signs alone, and without repeated estimation of the opsonic index; the second, and even more important, the superior results that follow when the patient is treated by means of a vaccine prepared directly from the responsible organism

cultivated from his own lesion as compared with those obtained when a "stock" vaccine of the causative bacterium is employed.

In the treatment of bacterial infection, therefore, the first proceeding is to identify the particular organism which is causing the diseased condition, and to isolate it in pure culture. This, of course, is done by the ordinary methods of bacteriological investigation. The next step is the preparation of the vaccine, and a short description of the method of performing this important operation may prove of interest.

METHOD OF PREPARING VACCINE.

A slope culture on agar incubated at 37° C. for not more than eighteen hours of the particular organism is used. About 2 c.c. of distilled water are poured into the tube containing the growth, and the whole of the growth is then scraped off with a platinum rod and evenly suspended in the distilled water, so that a turbid emulsion is prepared. The emulsion is then transferred to a sterilised test tube and well shaken up with some glass beads to break up any clumps as far as possible. Finally, as an extra precaution, the emulsion is passed through a sterilized filter paper into another sterile test tube. It is now necessary to estimate the number of cocci or bacilli present in the emulsion and make it up into the required doses. The doses usually given are 250, 500, or 1000 million organisms, and these are contained in 1 c.c. or 0.5 c.c. as is thought fit. The two ways usually employed in estimating the number of organisms present are the following:—

(1.) This method is the most rapid and the simplest; only a capillary pipette furnished with a teat and a glass slide being necessary; a mark is made on the pipette with a blue pencil, about a centimetre from the open end; after squeezing the teat, and forcing out some of the contained air, three separate and equal volumes of sodium citrate solution (1 per cent.) are sucked up into the pipette, then one volume of normal blood from a pricked finger, and finally, one volume of the bacterial emulsion. These five volumes are thoroughly mixed by repeatedly forcing them out on to a slide and sucking them up again into the pipette.

The mixture is finally spread in thin films on two slides and stained by Jenner's stain. Knowing that 5,000 millions red blood corpuscles are contained in 1 c.c. of normal blood, the number of organisms present in 1 c.c. of the emulsion can readily be estimated by averaging the ratio of red corpuscles to bacteria in several fields under a $\frac{1}{12}$ in. oil immersion lens. If the number of organisms present in 1 c.c. of the emulsion is known, then by measuring the volume of emulsion already prepared the number of bacteria present in this can be determined, and the dilution necessary to give the required number of bacteria per cubic centimetre or half centimetre, as required, can easily be carried out.

E.g., in three fields counted the red cells averaged 250 and the bacteria 100, then

$$\begin{array}{rcl} 250 & : & 100 & : & 5,000 \text{ millions} & : & x \\ * & x = & \frac{5,000 \text{ millions} \times 100}{250} & = & 2,000 \text{ millions} \end{array}$$

(2.) This method takes longer and needs more apparatus, but is undoubtedly the more accurate, though accuracy, where such large numbers are involved, is not absolutely essential.

In a graduated pipette take—

- (a) 1 c.c. of the emulsion and add 9 c.c. of sterile water, mix well in a glass capsule.
- (b) Take 1 c.c. of (a) and add 9.9 c.c. of water = 1 in 1000 dilution.
- (c) Take 1 c.c. of (b) and add 9.9 c.c. of water = 1 in 100000 "
- (d) Take 1 c.c. of (c) and add 9.9 c.c. of water = 1 in 10000000 "
- (e) Take 1 c.c. of (d) and add 9.9 c.c. of water = 1 in 100000000 "

Now take 0.2, 0.3 and 0.5 c.c. of (e) and mix each amount with the contents of a tube of melted agar and pour into Petri dishes. Repeat this process with similar quantities of dilutions (c) and (d). Incubate the plates at 37° C, and twenty-four hours after, count the number of colonies which have developed, calculate the number of organisms per c.c. and dilute the emulsion down to the required dose. In the meantime the crude emulsion has been

* There are two thousand millions bacteria present per c.c. of crude emulsion, and if the dose required is 500 millions, then to make 1 c.c. doses, the whole amount needs diluting three times.

killed by heating for an hour at 60° C., and when the emulsion has been diluted 25 per cent. Tricresol is added.

The organisms responsible for various pathological lesions for which corresponding vaccines have been made and used are comprised in the following list :—

Staphylococcus pyogenes aureus.	Bacillus coli communis.
Staphylococcus pyogenes albus.	Bacillus pestis.
Streptococcus longus.	Bacillus anthracis.
Bacillus dysenteriae.	Bacillus typhosus.
Bacillus pyocyaneus.	Vibrio cholerae.
Pneumococcus.	Gonococcus.
Micrococcus melitensis.	Friedlander's bacillus.

CHOICE OF CASE FOR TREATMENT.

Only those patients affected with a chronic bacterial disease are suitable for treatment by a vaccine. A patient having chronic suppuration from a diseased joint, or an empyema, or a skin disease, such as furunculosis or acne, gradually loses all the opsonin for that particular organism concerned in the production of the disease, and so the phagocytes are unable to act on the offensive. Now, by injecting the dead bodies of that same organism into some unaffected area of subcutaneous tissue, a fresh stimulus is given, which provokes the formation of an increased quantity of opsonin—and this without involving the least danger for the patient.

To illustrate the most suitable kind of case to choose, I subjoin a list of those treated at Guy's Hospital during the last nine months.

- 7 cases of Acne Indurata.
- 2 cases of Furunculosis.
- 1 case of Supraorbital Suppuration.
- 1 case of Frontal Sinus Disease.
- 1 case of Gonorrhœal Rheumatism.
- 1 case of Gonorrhœal Epididymitis.
- 2 cases of Chronic Gleet.
- 1 case of Psoas Abscess (also treated with Tuberculin, died).
- 1 case of Multiple Abscesses.

- 1 case of *Acute Infection of the Ankle Joint* (amputated).
- 1 case of *Acute Cellulitis of the Arm*.
- 1 case of Chronic Suppuration of the Elbow Joint.
- 2 cases of Chronic Suppuration of the Ankle Joint.
- 1 case of Suppurating Stump after Amputation.

Although I have included in this list two acute cases, yet I do not think they were the right kind of case to treat, for the injection of more poison into a patient who has not yet had time to react against the large amount thrown into the system from the primary infection appears logically incorrect.

With regard to the patients treated with a vaccine prepared from the *Gonococcus*, only one did well, and that was the one with gonorrhœal epididymitis. The vaccine used in these cases, however, was one prepared from an old "stock" cultivation from the laboratory which had been replanted many times, and so most likely had lost its virulence. It is intended to treat future gonorrhœal cases with a vaccine prepared directly from the patient's own strain of *Gonococcus*, or in cases where such a course is impossible, to employ a recently-isolated *Gonococcus* in the preparation of the vaccine.

GENERAL PROCEDURE.

The first series of cases had the opsonic index estimated twice a week; later it was estimated but once a week, and now no opsonic index is determined except in the case of tubercle. The patient was also kept in bed for twenty-four hours after the first inoculation, but this, as rather an unnecessary precaution, is now omitted, as I have never seen untoward effects follow the injection of a vaccine, whether the patient be kept in bed or not. In the case of tuberculin injections, however, when the index is very low, it is quite conceivable that the patient might develop general tuberculosis; and I have seen a case in which a rise of temperature as high as 103° F. followed a dose of .0002 mgr. of Koch's T.R. Reactions such as these are not to be feared at all in the case of vaccines other than tuberculin.

I usually inject the required dose into the subcutaneous tissue just below the costal margin with an ordinary sterilized hypodermic needle.

Vaccines as an Aid to Surgery and Medicine.

THE INDICATIONS FOR THE SECOND AND FOLLOWING DOSES.

When the opsonic index is taken after the injection of a vaccine, there is a definite oscillation of the curve.

The index is at first, say, at .8, then after the injection it falls to a lower level, say, .4, generally being at its lowest twenty-four hours after the injection, this phase being known as the negative phase. After this, as the patient reacts, the index begins to rise, and the positive phase occurs; there may be one or two slight rises and falls, but the index eventually ends at a higher level than that at which it started. An inoculation must not be given during the negative phase, or the index will fall still lower, and the positive phase will be very slight or altogether absent; but if the patient be injected during the positive phase, there will be a slight negative phase again, and then a positive phase higher than the first one. What one aims at is not to give an injection during a negative phase, so that the positive phases may be superimposed on one another, and a high level thereby reached. Now, when patients are injected with vaccine other than tuberculin, the negative and positive phases can often be well judged by clinical signs, especially when it is known from early cases where the index was taken; that from the time of the inoculation to the top of the curve takes about two to three weeks.

In the negative phase in acne there is very often a fresh crop of boils, and in gleet an increased urethral discharge. At times, after the second week, the patient will come and say that he feels that he is running down and wants another injection. So experience shows that if a patient is injected between the fourteenth and twenty-first day he will do just as well as if his opsonic index had been taken and the patient injected at the top of the rise. Besides, even when the opsonic index is taken, the positive phase may be missed through not taking the index often enough. In patients other than hospital patients, having a vaccine made and having the opsonic index taken every week is an expensive process, and it brings the treatment within easier reach of the middle classes, if, when the vaccine has

once been made, there is nothing more to be done but have an injection once in three weeks. If the clinical signs get worse after a dose and last for some time, then the dose has been too large; if, on the other hand, very little negative reaction takes place, a larger dose may be given; 250 millions is the best dose to start with, and this can be increased to 500 millions, and later on 1000 millions may be given with absolute safety.

DURATION OF THE TREATMENT.

This varies considerably, and depends chiefly, of course, on what the patient is being treated for. One cannot expect to quickly get rid of a disease which has been going on for years, and it is these very chronic bacterial diseases which do best with vaccines. To illustrate the great variation of time taken to get rid of some of these infections, I will quote two cases. The first, a case of multiple abscesses in a child ten months old. Seventy-five of these abscesses had been opened at different times. One injection only was administered, and yet at the end of three weeks the little patient was so well that he could leave the hospital. The other, a case of *acne indurata*, was injected every three weeks for seven months, and at the end of that time he at last got rid of his disease, not a single spot being left; however, for safety's sake, he was injected at the end of the eighth month again. As I shall be giving all the cases in detail later, it is unnecessary to give more instances; it but remains to be said that nearly every case treated by a vaccine has shown some improvement, and of those cases that completely recovered, none have, so far, had any signs of recurrence. I would strongly urge that this treatment should always go hand-in-hand with the corresponding medical or surgical treatment, for it is but an aid to medicine and surgery, and though alone it may do good, still, I think it should, as far as possible, be combined with other treatments which are deemed necessary.

CONCLUSIONS.

The conclusions to be drawn from the past year's experience may be summarised as follows:—

1. The disease must be chronic, not acute, to be really benefited by the treatment.
2. The patient must be treated by a vaccine prepared directly from the invading organism.
3. The patient must be injected every three weeks if no opsonic indices are taken.
4. The vaccine must be used in conjunction with other treatments as far as possible.
5. The treatment must be persisted in for at least six months if at first it is not successful.

I wish to thank Dr. Eyre for his constant oversight and direction of my work, and for his trouble in correcting the proofs of this paper.

LIST OF CASES.

CASE 1.—H. G. G., æt. 24, male. Acne indurata of several years' duration, affecting the face, neck, and back, and due to staphylococcus aureus; he had about eight injections, the last being given six months ago. There has been no recurrence.

CASE 2.—C. E. T., æt. 28, male. Acne indurata due to staphylococcus albus. He improved a great deal after six injections and has remained almost free from pustules.

CASE 3.—H. T., æt. 22, male. Acne indurata due to staphylococcus albus. He improved slightly after five injections.

CASE 4.—S. J., æt. 24, female. Acne indurata of four years' duration and due to staphylococcus albus and aureus; she improved considerably with three injections of albus and four of aureus, and after six injections of each became entirely clear. She had her opsonic index taken, and was injected separately to each organism. In treating such a case again it would save time and trouble to inject with a mixture of staphylococcus aureus and albus vaccine. No pustules have appeared, though she has had no injection for four months.

CASE 5.—H. E., æt. 26, male. A very bad case of acne indurata, the whole chest and back being covered with pustules due to staphylococcus aureus. He had two injections of 250 millions, two of 500 millions, and one of 1000 millions. A great improvement has taken place. He is still under treatment.

CASE 6.—J. B., æt. 22, male. A few bad spots of *acne indurata* on the face. He was completely cured with two doses of *staphylococcus albus* vaccine.

CASE 7.—T. T., æt. 25, female, with *acne indurata* caused by *staphylococcus albus*. She has been given several injections and is a great deal better.

CASE 8.—H. M., æt. 25, male. He had several boils on the back of his neck due to *staphylococcus aureus*. Since the first injection there has not been a boil. He was given three injections and remains well.

CASE 9.—B. Z., æt. 24, female. Small boils due to *staphylococcus albus* and aureus were present on the face; no more have appeared since the first injection. She was given one injection of 250 millions and two of 500 millions.

CASE 10.—R. R., æt. 3, female. Supraorbital suppuration. She reacted well to injections, several small sequestra were removed by operation, and eventually she was sent out with the wound quite healed.

CASE 11.—F. C., æt. 39, female. Empyema of frontal sinus due to *staphylococcus albus*; she had severe frontal headache and nasal discharge for four or five months before admission to the hospital; on December 15th she had her first injection, and during the positive phase the anterior ends of her middle turbinate bones were removed under an anæsthetic. By January 12th her headaches were almost gone and the discharge was very much less. She left the hospital with a very slight discharge.

CASE 12.—A. B., æt. 35, male. Gonorrhœal rheumatism. This man showed a slight improvement after one injection, but was sent out of the hospital and lost sight of.

CASE 13.—B. C., æt. 24, male. Gonorrhœal epididymitis and gleet. After three injections of a gonococcus vaccine, both the epididymitis and gleet cleared up.

CASES 14 & 15.—Chronic gleet. Neither of these cases showed any improvement after six injections; perhaps this was due to a faulty vaccine.

CASE 16.—J. T., æt. 21. Extensive psoas abscess, which was opened and drained on June 29th, 1905; a sinus persisted and discharged profusely for months; the pus contained *staphylococcus aureus*. On December 15th, injections of *staphylococcus aureus* vaccine and tuberculine were started, but he did not react well. The opsonic curves were very irregular, and both the curve for tubercle and that for *staphylococcus aureus* underwent similar changes throughout. He died on February 4th.

CASE 17.—B. J., 10 months. This child had multiple abscess all over the body. The pus was found to contain *staphylococcus aureus*, and a vaccine was made. The child was in extremis at the time it was injected, the seventy-fifth abscess having been opened. After the first and only injection the patient began to mend, and at the end of three weeks was quite well. No more abscesses appeared, nor did the child need a second injection.

CASE 18.—M. A., æt. 45, female. This patient in an accident had her ankle joint opened and infected with *streptococcus longus*. The question of amputation was discussed at the time. Only one dose of the vaccine had been injected when the leg was amputated. The woman made a good recovery.

CASE 19, æt. 23, male.—An acute cellulitis of the arm, the organism being *streptococcus longus*. A vaccine was made and a few days after the

injection the patient improved and was sent out well. I think his rapid recovery after the injection was not in any way due to the vaccine. It was not likely that the vaccine could have acted in the time, and the man's infection was much too acute for any vaccine to have done any good.

CASE 20.—E. L., æt. 58, male. An empyema caused by the pneumococcus of Fränkel, and an abscess in the elbow joint caused by the streptococcus aureus were the offending lesions here. The patient has been injected three times with a staphylococcus vaccine, and is now beginning to get better.

CASES 21 & 22.—Both males. The ankle joint was opened by an accident and became infected with staphylococcus aureus. Both cases were given about six to ten injections and eventually recovered.

CASE 23.—X. W., æt. 37, male. He had his arm amputated for necrosis of the humerus. The stump suppurated and, after several operations, as pus was pouring away from the wound, it was decided to make a vaccine. He had three injections at intervals of three weeks, and was sent out with the wound quite healed.

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PYELONEPHRITIS

AS A COMPLICATION OF PREGNANCY.

By G. BELLINGHAM SMITH.

PYELONEPHRITIS as a complication of pregnancy is by no means of great rarity, if we are to judge by the number of cases that have been recorded of late years. Since 1901 I have seen seven patients suffering from this lesion. Three of these I have already recorded (*Journ. Obs. and Gyn.*, Aug., 1905). During the past year three more cases have occurred amongst the obstetric out-patients, and of these I give the notes of two that were watched throughout the attack.

CASE 1.—R. H., aged 38 years, the mother of seven children, came to the obstetric out-patient department on September 26th, 1905, complaining of weakness and fever associated with pregnancy that was nearly full time. Her illness commenced nearly six weeks previously, in the eighth month of pregnancy. She complained of pain in the right side, and was seen by Mr. A. M. Webber, the obstetric resident, who found much albumen in her urine. He visited her at her home, and three days later, hearing fine crepitations at the right base, diagnosed pleurisy. She appears to have improved in ten days' time, so that she was enabled to get about her work. A month later Mr. Webber was asked to see her again. She had had a rigor and had a temperature of 103.2°. Fine râles were again heard at the right base, and it was again thought that she was suffering from some pulmonary or pleural lesion.

When I saw her she was thin and cachectic, and looked very ill. Her pregnancy was about full time, the presentation being a vertex in the L. O. A. position. The foetus was alive, and the foetal heart-beat was 140. The patient's tongue was dry, and she had some herpes on her lips which served to further suggest that she was suffering from some pulmonary lesion. On examination of the chest nothing could be heard but a few fine râles at the right base. The temperature was 101.2° , the pulse rate 132, the respirations 32 to the minute. She complained of pain in the right loin and was tender when pressure was made over the kidney. On examination of the urine there was found a small amount of albumen, and microscopically pus cells were seen. There was no frequency of micturition, nor was there any tenderness over the bladder.

The temperature oscillated between 97.4° and 102° for the next four days when, on September 30th, she was delivered of a full-time living child, weighing five pounds thirteen ounces. She continued to look ill all this time, and the urine, which was acid, contained pus. The amount of urine passed varied from eighteen to twenty-eight ounces daily, though it is probable that some was lost during the action of the bowels.

On October 2nd, she had a rigor. The temperature still showed daily elevations to 100° — 101° .

On October 3rd, the temperature rose to 103.4° , and at 2 a.m. the following morning she had another rigor. The uterus was involuting well, and there was no evidence of any septic infection. She complained of her throat being dry and swollen. The urine, which was acid and of a low specific gravity, 1005, contained pus, granular and hyaline casts. A specimen of urine which had been drawn off previously into a sterile tube, and had been examined bacteriologically, was reported to contain bacillus coli communis. The temperature continued raised till October 11th, reaching 103.2° on the 8th. On the 12th it fell to normal, and after one or two elevations to 100° remained normal.

On the 9th, she developed a blotchy erythematous rash on her trunk and limbs. The throat was dry and the tongue foul. On making a vaginal examination, I found the vagina moist, the

secretion colourless and without odour, the uterus involuted well and free from tenderness. In fact, there was no evidence of any septic lesion of the pelvic organs. She complained of pain in the right side. The urine still contained pus, but there were no casts, and the amount found was larger, being about thirty-five ounces. From this point she rapidly improved. The rash disappeared in a day or two; by October 12th, the temperature had fallen to normal, and the urine examined on this date showed no pus. She was discharged well on October 22nd. She was seen by Mr. Webber in January, 1906, and I saw her again three months later. There was on neither occasion any albumen or pus in the urine.

This was a severe case of pyelonephritis, the kidney substance being probably more affected than is usual. It presented considerable difficulty in diagnosis. Although the urine was known to contain a little albumen, the severe general condition of the patient, the pain felt over the lower part of the right chest, and the herpes, would suggest to one who was not aware of this particular complication of pregnancy, a pulmonary rather than a renal lesion. There was a sharp recurrence shortly before labour, the attack persisting for eleven days after the confinement.

One feature, I think, that is unusual in a case of this severity is the rapid subsidence of the pus in the urine. This almost invariably persists after the fall in the temperature, but in this case the two coincided.

CASE 2.—L. H., aged 30, came to the out-patient department, October 19th, 1905, on account of pain in the right side, associated with pregnancy. She had had six children and five miscarriages, and there had been no trouble with any of her previous confinements. In September she went into the country "hopping." Whilst away she lost for a day or two some blood per vaginam. This ceased, and she went on with her work. She returned home and was well until October 13th, when she was seized with cold shivering, and developed suddenly a pain in the right side. This continued for three days, when she came up to the front surgery, where it was thought that she

might have some pleurisy. She was very constipated at the time, was not sick, but retched occasionally.

When I saw her on October 19th, the uterus reached to half an inch above the umbilicus. The temperature was 101.8° , the pulse rate 132. There was pain in the right loin extending round to the front of the abdomen and down into the right iliac region. There was tenderness on palpation over the right kidney. There was no tenderness over the bladder, or frequency of micturition. The urine was acid, specific gravity 1013. There was a trace of albumen, no blood, and pus was detected on a microscopical examination.

She was admitted under the care of Dr. Hale White into Clinical ward, when she was put on milk diet, warm applications to the loin, and urotropine. A catheter specimen of the urine was obtained for bacteriological examination, and showed a pure culture of bacillus coli communis.

As the result of treatment she gradually improved. By October 31st the pain was much better, and had disappeared altogether from the loin by November 4th. On this date very few pus-cells were detected in the urine, and none were discoverable at the time of her leaving the hospital on November 10th. The temperature showed daily elevations reaching 101° to 101.8° for ten days after admission. It then fell to normal. Pulse and respiration showed corresponding elevations. There was no interference with the course of pregnancy.

These two cases show well the chief symptoms of pyelonephritis complicating pregnancy:—the sudden onset of pain in the right side associated with rigors, and pyuria, clearing up in one case without interruption of pregnancy; in the other and more severe case after delivery at full term.

Our knowledge of this complication is comparatively recent. Rayer mentioned it in 1841 (*Traité des maladies des reins*), but it was not till 1889 that it began to receive the attention it deserves. In that year Kruse, in an inaugural dissertation (Wurzburg) to which I have not been able to refer, drew attention to the subject. Three years later it was brought forward more prominently by Reblaub who, in a short paper containing five

cases, drew the attention of the French Congress of Surgery to a "mode of urinary infection which had so far escaped the attention of surgeons" (Congrès français de Chirurgie, 6th Session, Paris, 1892.)

Vinay from time to time brought forward cases which confirmed Reblaub's original observations, and finally in 1899, with A. Cade, reviewed the whole subject in a paper which has formed the basis of all subsequent work (*L'Obstétrique*, 1899, Vol. iv., p. 230).

Etiology. — The factors concerned in the production of pyelonephritis were first pointed out by Reblaub. In his communication he drew attention "to a mode of urinary infection that had so far escaped the attention of surgeons, namely, infection of the kidney and pelvis following on compression of the ureter and consequent renal retention, more especially as the result of compression of the ureter by the gravid uterus."

Of the predisposing causes compression of the ureter is undoubtedly the most important. Dilatation of the ureter as the result of pressure by the gravid uterus has been noted by many observers in patients dying in the course of pregnancy or in those recently confined. This pressure is exercised to a greater extent on the right than on the left side. Olshausen, in twenty-five cases in which dilatation of the ureter had been noted, found one side alone affected in twelve, and of these ten were on the right side. Corresponding to the greater liability to compression that the right ureter presents, we find pyelitis in recorded cases confined almost entirely to the right kidney. The ureter is compressed at the brim by the gravid uterus, the dilatation being above this point. The pressure is not exerted by the lower pole of the foetus, or we should find pyelonephritis more frequent in the last two months of pregnancy.

That it is due to the gravid uterus is generally accepted, though why it is so much more frequent on the right side is not quite clear. Opitz (abstract in *Journ. Obs. and Gyn.*, Vol. viii., p. 327) explains it by the right obliquity of the uterus. Cumston (*Journ. Obs. and Gyn.*, Vol. viii., p. 223) describes the mode of production

as follows: "While the pregnant uterus develops, its borders come nearer to the ureters, which they displace and push over to the bones of the pelvis, upon which it compresses them. The uterus develops much more to the right than to the left, and inclines to the former, and besides this it undergoes a rotation on its vertical axis and turns in the direction of its greatest development, that is to say, to the right, thus freeing the organs on the left side and exerting a greater compression on those of the right." Cathala considers that it is due to the traction exerted by the lower uterine segment on the ureter.

Amongst other predisposing causes, cold and fatigue appear to have played a part in certain cases. Vinay, for instance, records a case in which the illness followed a fatiguing walk in cold weather, and another where a patient experienced a sensation of chill in coming out of a bath.

Bonneau thought that any condition that would increase pelvic compression was to be regarded as a predisposing cause, such, for instance, as hydramnios and contracted pelvis. Though one might accept this as theoretically probable, in none of the recorded cases that I have seen does there appear to have been any such abnormality. In a case recorded by Cumston (*loc. cit.* Case 9), pregnancy was complicated by an ovarian cyst the size of a large orange which pushed a six-months' gravid uterus somewhat to the right. The increased pressure in this case may have been responsible for the pyelonephritis which affected both kidneys. A further predisposing cause was possibly the lowered vitality that attended the operation for the removal of the tumour. Apart from pregnancy, I have known pyelonephritis occur on two occasions in the course of convalescence from an abdominal operation, in one instance for the removal of a fibroid, in the other an ovarian cyst. In the latter case the illness was ushered in by a sharp gastro-intestinal attack.

The exciting cause in the great majority of cases is the bacillus coli communis. This organism was present in pure culture in the seven cases I have seen, and amongst others recorded in which a bacteriological examination was made, I have only met with one in which this organism was not found. In this case,

which was reported by Vinay (No. 6), streptococcus was shown to be present. This case was clinically of the same type as the others.

Infection is possible by three routes, the blood stream, the lymphatics, or inflammation ascending from the bladder. In the cases under consideration infection takes place undoubtedly by the blood stream. Opitz favours the view that it takes place by an ascending inflammation from the bladder. He states that the female urethra always contains organisms, and that the bladder in pregnancy is very liable to cystitis. Under normal conditions the valve-like opening of the ureter into the bladder protects the former from infection. When dilatation of the ureter occurs, there is a free communication between the latter and the bladder, and organisms readily pass into the ureter.

There are two objections to this view—one anatomical, the other clinical. The ureter appears to be dilated, not in its whole extent, but only above the brim of the pelvis, in which situation it is compressed. The lower part of the ureter, not sharing in the dilatation, there would be no increased liability to the entrance of organisms from the bladder. The clinical objection is still greater. In none of the cases I have seen was there any evidence of preceding cystitis, and the same may be said of those cases recorded by others that are typical of this complication. That infection may occur by this route is undoubted, but the whole clinical course of the disease is different. The chief feature of pyelonephritis in pregnancy is the presence of pus in the urine, without any symptoms pointing to cystitis. Lymphatic infection has been invoked to explain those cases occurring during the puerperium.

Such cases appear to be rare; they are possibly different in their mode of development. Experiments have been performed to show the possibility of infection by the blood stream. Bonneau and Reblaub ligatured the ureter and injected pure cultures of bacillus coli communis or staphylococcus into the blood. To those of Bonneau I have not had access. The experiments of Reblaub are wanting in detail, but he appears to have set up pyonephrosis by this means.

On account of the frequency of infection with the bacillus coli communis, most French observers have considered that a relationship exists between the pyelitis and some intestinal trouble, and in proof of this they point to the frequency of constipation or diarrhœa in these cases. In some of those recorded the diarrhœa appeared to coincide rather with the onset of symptoms than to precede them, and constipation is so common a symptom in pregnancy that it is difficult to know what stress is to be laid on it as a factor. In an obscure case reported by Jeannin and Cathala (Bull. Soc. d'Obs. de Paris, June, 1905), with some toxic symptoms, constipation lasted for fifteen days. The time of onset of the pyelitis and its relationship to the constipation is not quite clear. There is no doubt that many of the cases complain of constipation, and whether we regard it or not as promoting the liberation of the colon bacillus, it would assist in lowering vitality.

Vinay was of opinion that pyelonephritis occurred more frequently in multiparæ than in primiparæ, but a larger number of cases than he dealt with has not confirmed his view, and it is now generally held to be more common in primiparæ. It is met with at any age within the child-bearing period, though the largest number, as might be expected, occurs between twenty and thirty.

The onset of this lesion occurs most often between the fifth and eighth months of pregnancy. Potocki recorded one that commenced at the end of the third month, and in one or two the first appearance of symptoms was noted in the 9th month. Viney considered that it commenced earlier in primiparæ than in multiparæ, but I have not found much difference in the incidence of this affection in the two classes.

Symptoms.—A characteristic of most cases is the sudden onset of the illness. Not infrequently it is ushered in with a rigor which may be repeated. The temperature rises rapidly, and may reach 103°–104°, being accompanied by all the ordinary symptoms of fever.

At the same time pain is felt in the right loin, and may extend along the course of the ureter to the right iliac region and bladder

or down into the right thigh. Occasionally it is not complained of for a day or two after the onset of general symptoms. The pain shows exacerbations and may at times intermit, owing no doubt to the occasional relief of pressure. The urine is of the febrile type, acid, scanty, and high-coloured, and when first examined contains as a rule both albumen and pus. It may be so diminished in amount as to suggest considerable derangement in the functions of one kidney. In the first case described above there was marked diminution in the amount of urine secreted, associated with a grave disturbance of health. It is seldom that one has an opportunity of examining the urine at the commencement of an attack, but in one case in which Vinay (Obs. 6) was able to do so, it showed the presence of albumen alone.

Though increased frequency of micturition is at times noted, it is not associated with such symptoms as tenderness over the bladder, pain on passing water, or alkalinity, as would point to the presence of cystitis. It has been already pointed out that primary cystitis, followed by ascending pyelonephritis, presents a different clinical picture altogether. Cystitis may, however, follow on the kidney affection, an example of this being given by Vinay (Obs. 8).

Pressure over the right loin causes severe pain, and this is occasionally elicited by pressure along the course of the right ureter. The kidney may occasionally show evidence of enlargement. Some authors speak as though this were the rule. Craigin (*Trans. Am. Gyn. Soc.*, 1904, Vol. xxix., p. 26) says that the kidney can usually be felt enlarged and tender. With this I do not agree. Of the seven cases I have examined I could feel the kidney in one only, and in this case I thought it might be enlarged. The difficulties of palpation are due in the first instance to the rigidity of the abdominal muscles over the tender organ, and secondly to the presence of the pregnant uterus. It is further by no means so certain that the dilatation of the pelvis is sufficient in most cases to render the organ more palpable than under normal circumstances.

The temperature undergoes wide oscillations daily, falling gradually to normal. The most acute symptoms generally last

about a week to ten days. The temperature may, however, persist for some time after the subsidence of pain, showing daily elevations of 100° – 102° for two or three weeks.

The pyuria is still more variable. It almost invariably persists after the acute symptoms have subsided and the temperature has fallen to normal. It usually lasts from two to six weeks, though in some cases it has run a much longer course. In one case reported by Reblaub it lasted for four months, but the patient had developed a pyonephrosis, which was operated upon at the end of this time. On an average, the duration of the pyuria appears to be roughly three to four weeks. Pus has been noted to disappear altogether for a time from the urine, owing to the complete blocking of the ureter.

There may be a relapse during the same pregnancy. In the first case given above, there appears to have been a relapse a month after the onset, though it is not known whether the urine was clear of pus during the interval. It may return with successive pregnancies. Vinay gives a good example (Obs. 1) where pyelitis recurred on four occasions.

There is a very wide range in the severity of symptoms in different cases. In some, no doubt, it is overlooked altogether or regarded as a different complaint. Of the two cases recorded above, one was a mild one, the attack lasting about four weeks and being unassociated with any severe general symptoms. The other was more serious, and the patient was wasted and cachectic. Drowsiness has been noted occasionally and even coma. A patient, admitted to Guy's Hospital in 1901 (*Journ. Obs. and Gyn.*, Aug., 1905, case 1), was very drowsy for a time. Jeannin and Cathala (*Bull. Soc. d'Obs. de Paris*, June, 1905; abstract *Journ. Obs. and Gyn.*, Jan., 1906) report a case that ended fatally and was so obscure that the diagnosis was only cleared up at the autopsy. When seen first, the patient was in a state of stupor, suffering from severe headache with violent exacerbations, raised temperature, rapid pulse, and constipation which had lasted fifteen days. Aperients led to the passage of abundant fæces with fœtid odour, but without improvement in the condition of the patient. The urine contained no albumen and no pus.

There was optic neuritis and several retinal hæmorrhages. Death occurred three weeks after admission. At the autopsy the kidneys were voluminous, and a quantity of purulent fluid escaped from the pelves, which were dilated. Abscesses were present throughout the kidneys, and a bacteriological examination showed the presence of the bacillus coli communis in pure culture. The presence of pus was possibly overlooked in this case owing to incontinence of urine which existed during the fortnight preceding death.

Intense dyspnœa existed in a case reported by Potocki (Cumston, *loc. cit. supra*) and the local pain was so severe as to suggest the possibility of a perinephritic abscess.

Effect of pyelonephritis on the course of pregnancy.—Opitz states that in twenty-three cases out of fifty-three in which the result was known, premature labour occurred spontaneously. I have little doubt that this proportion is much too high, and that it is due to the inclusion of a number of isolated cases reported on account of the severity or unusual character of the symptoms. If one takes those cases reported in series by two or three observers the results are very different. Of twenty-seven cases I have collected in which the results are known, premature labour occurred in four only. In three of these it was due to the severity of the attack, occurring two or three days after its onset, or in the course of a relapse. In the fourth case the labour, which occurred at six and a half months, was predisposed to, in all probability, by a blow on the abdomen a fortnight before the onset of the pyelonephritis, the placenta on delivery showing an old adherent blood clot.

In the majority of cases, in sixteen out of the twenty-seven, the condition cleared up before the onset of labour. The symptoms subsided, the pus disappeared from the urine, and pregnancy did not appear to be affected in any way by this complication.

In a case recorded by Bué, though the pus disappeared there was persistence of albuminuria till labour occurred at term. Persistence of albumen in the urine after the subsidence of pyuria

is rare, and Vinay states that he has not noted its occurrence in any of his cases.

In the remaining cases, seven out of the twenty-seven, the symptoms persisted till labour at full term. In these, the onset of the pyelonephritis took place in the last two months of pregnancy.

It would appear that when pyelonephritis supervenes before the last two months of pregnancy, there is a great probability of its clearing up before labour, and further, that premature labour is likely to occur in those cases that are attended by severe initial symptoms, and to follow closely the onset of the attack.

Effect of labour on pyelonephritis.—From the point of view of treatment, it is important to know what effect emptying the uterus has on the pyelonephritis. In those cases in which labour occurs prematurely, the condition usually clears up within a short time. The temperature falls to normal generally within a week, and the pus disappears from the urine within a fortnight. The following case, admitted to Guy's Hospital in 1901, is a good example (*Journ. Obs. and Gyn.*, August, 1905). Sarah H., aged 18, was admitted suffering from pyelonephritis. She had all the usual symptoms—fever, pain in the right loin and pyuria. These persisted without very marked improvement for four weeks, when labour occurred spontaneously at six and a half months. The symptoms cleared up rapidly after the confinement, the temperature falling to normal on the day following and the pus disappearing from the urine by the ninth day. Here the effect was so marked, and followed so promptly on delivery, that one is justified in attributing it directly to the emptying of the uterus. The same result has followed on induction, though as this is likely to be undertaken in the more severe cases only, one might expect to find occasional exceptions. Such an exception is afforded by a case reported by Cumston (*loc. cit.*, case 11). A woman, aged 37, the mother of four children, was found, when five months pregnant, to have an ovarian cyst on the left side, the size of an orange. This was removed, the convalescence being uneventful till the seventeenth day after the

operation, when pyelonephritis was ushered in with chills and raised temperature. Her general condition became serious, and three weeks after the onset of the attack, artificial delivery was performed. There was slight improvement for a day or two, followed once more by high temperature and large quantities of pus in the urine. She developed pain in the left renal region, the kidney being palpable. As no improvement took place, the kidney was explored a fortnight after the confinement. It was found greatly enlarged and congested. The right kidney was also exposed and the pelvis found dilated to four or five times its normal size, and filled with a purulent fluid. The patient died the next day. This case was complicated by the operation of ovariectomy, and was severe from its onset, the artificial delivery producing very little, if any, effect on the course of the disease.

As the first case reported above shows, a good result may follow labour at full term. Here, in spite of the severe symptoms, the relapse and the cachexia, the temperature had fallen to normal, and the pyuria had disappeared within a fortnight of the confinement.

In the small number of cases so far reported, there seems, however, to be an undue proportion in which labour occurred at full term, and in which the kidney lesion did not clear up quickly. In one recorded by Vinay there was pus in the urine three weeks after confinement, the total duration of the pyuria at that time being six weeks. Reblaub published two cases in which apparently pyelonephritis supervened towards the end of pregnancy, and instead of clearing up after labour, ended eventually in pyonephrosis. As I have pointed out in a previous paper on this subject, neither of these cases is beyond criticism. In the first case, a primipara of thirty-nine, who passed through a difficult confinement, the urine was found to contain pus for the first time after labour. At the same time she complained of pain in the right renal region and was feverish. Four months later the right kidney was found to be enlarged and nephrotomy was performed.

Here the evidence respecting the date of onset of the pyelonephritis is unsatisfactory, and it is possible that we have in

this case an example of pyelitis occurring in the puerperium. The second patient, aged 38, and in her fourth pregnancy, had suffered pain in her right loin for a month preceding labour. She was thought to have cystitis. The urine remained purulent, and when seen a month later the right kidney was found to be enlarged and painful. Nephrotomy was performed and the patient died four days later. At the autopsy there was found to be a pyonephrosis on the right side, a hydronephrosis on the left.

Craigin (Trans. Am. Gyn. Soc., Vol. xxix., p. 122) describes the case of a primipara of 24, admitted at full term, stating that for two days she had suffered from pain in the right lumbar region and fever. The temperature was 102.4° , and the urine contained pus. She was delivered on the following day of a full-term child. In spite of treatment she grew worse, and a fortnight later the right kidney was removed. The kidney showed several small abscesses in its substance, and a bacteriological examination showed the presence of the colon bacillus.

These cases are sufficient to suggest that when the pyelonephritis originates towards the end of pregnancy, it is likely to be more severe than when occurring earlier, and further to present a tendency to persist after the emptying of the uterus, and to end in pyonephrosis or suppurative nephritis.

Prognosis.—Recorded cases lead to a more serious view being taken of this condition than is warranted. No doubt many slight cases are unrecognised, whilst the tendency is to publish those that are more serious or present special symptoms. Opitz thinks the condition should be looked upon as grave, as it causes some deaths and frequently prolonged, if not permanent, disturbance to health. I think he takes too serious a view of this complication. Whilst admitting that grave kidney lesions, or even death, may result, such accidents are rare, the great majority of cases recovering completely. As has been pointed out already, cases vary greatly in severity, many being slight throughout, whilst a few are attended by symptoms that may give cause for grave anxiety. We cannot judge by the severity of the onset what the subsequent course will be. Many cases, after a sharp initial attack, lasting, perhaps, a week, get well quickly. It is during this

stage that spontaneous delivery is likely to occur. It is rather on the persistence of symptoms that we must rely, when in spite of treatment the patient remains ill, and the pus in the urine shows no diminution. If, in addition, the patient becomes markedly cachectic, is drowsy, with persistent pain in the loin, and the kidney can be felt enlarged, the question will arise as to whether a more serious lesion in the shape of a pyonephrosis or suppurative nephritis exists. It would appear that those cases starting early in pregnancy are, on the whole, slighter and more amenable to treatment than those originating in the last two months, when presumably the pressure on the ureters is more severe and persistent. A grave significance attaches to those cases in which symptoms persist without alteration, or become steadily worse after the uterus has been emptied.

Diagnosis.—Unless the possibility of this complication is borne in mind, it is likely to be regarded, for a time at least, as one of several other conditions. Cystitis is commonly mentioned as one of these for which it is likely to be mistaken. This is true if the presence of pus in the urine has been discovered. More often this is not noted, for it gives rise in the early days of the disease to no more than a slight turbidity, and is thus not likely to attract the patient's attention. A mistake is more likely to occur in those cases in which there is some frequency of micturition and when the pain travels down to the hypochondriac region. In my experience, pyelonephritis is regarded more often in its early stages as some pulmonary or pleural lesion. The situation of the pain over the lower part of the right chest, more especially if a few râles can be heard, associated with an illness of sharp onset and some severity, is very likely to lead to a diagnosis of pleurisy or pneumonia.

Another condition for which it has been mistaken is threatened abortion. Guéniot (*abstract Journ. Obs. and Gyn.* Vol. ix., p. 46), who draws attention to the possibility of this error, reports two cases of pyelonephritis in the first half of pregnancy, in each of which the diagnosis of threatened abortion was made. The situation and character of the pain, when more closely studied, would serve alone to clear up any

doubt. Craigin thinks that the three conditions most likely to be confused with pyelonephritis are appendicitis, typhoid fever, and salpingitis. In two of his cases the point of greatest tenderness corresponded closely to McBurney's point, and appendicitis was suggested strongly. In each of them the diagnosis was effected by an examination of the urine. In one other of his cases the irregular fever and epistaxis led him to think in the first instance of typhoid fever. The diagnosis would be cleared up in any doubtful case by an examination of the urine and the discovery of pus in it. This routine should not be neglected in any case of pregnancy associated with pyrexia and abdominal pain.

Treatment.—Under suitable medical treatment the tendency of these cases, more especially when originating before the eighth month, is to recovery. Treatment consists in the main of rest in bed and warmth, with a milk diet and attention to the bowels. Of drugs urotropine appears to be the most useful, and should be tried in the first instance, a variation being afforded by benzoic acid and the salicylates. Turning the patient over to the left side to relieve the pressure on the right ureter has been suggested and might be tried. A high temperature and severe symptoms may in themselves bring about a cure by causing spontaneous delivery. Induction of labour is seldom called for. Persistence of symptoms and a severe general condition might, however, call for more active interference.

Under these circumstances the question of inducing labour would have to be considered. We have an alternative choice, in those cases in which enlargement of the kidney points to pyonephrosis, in the operation of nephrotomy. This has been done in a case reported by Bebrax (Cumston, *loc. cit. supra*). The patient aborted, however, shortly afterwards. I think that where interference is called for, the uterus should be emptied first. In most cases the relief thus afforded to the ureter will lead to drainage of the dilated pelvis and subsequent recovery. Nephrotomy should be reserved for those cases in which no relief has been afforded by delivery, either prematurely or at full term. The necessity for this operation is shown by

such cases as those reported by Reblaub and Cumston. In one of Craigin's cases the kidney was removed, as the patient became worse after delivery, in spite of treatment on the usual lines. The justification for this line of treatment was shown by the presence in the kidney of numerous abscesses. Where diagnosis is effected early, and treatment on strict medical lines is carried out, such severe measures, however, as nephrotomy or nephrectomy will seldom be called for.

THE PATHOLOGY AND TREATMENT OF ŒDEMA :

WITH SPECIAL REFERENCE TO THE INFLUENCE
OF DIMINISHED EXCRETION OF SODIUM CHLORIDE
ON ITS PRODUCTION.

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It has long been known that during the formation of œdema and effusions into serous cavities less salt is excreted by the kidneys than is absorbed from the food. Until recently no great importance was attached to this fact, as the retention of salt in the body was considered to be merely the natural accompaniment of the retention of fluid brought about by various independent causes. During the last few years, however, a more thorough investigation of the subject has led Achard¹ and Widai² in France, and Strauss³ in Germany, to suggest that the retention of salt is not always secondary to that of water, but may in certain cases be primary and the cause of the latter.

¹ Presse médicale, 11th Sept., 1901.

² Journ. de Physiol. et de Path. Gén., v., 1107, 1903, and Arch. Gén. de Med., p. 1293, 1904, contain a résumé by Widai of his many papers on the subject.

³ Therapie der Gegenwart, Okt., 1902, Mai and Okt., 1903, Dez., 1904.

I.—RENAL ŒDEMA.

A normal man can excrete between twenty and thirty grms. of salt taken in the course of one day in the next forty-eight hours. Patients suffering from those forms of renal disease such as granular kidney, which are not associated with œdema, excrete it equally well. On the other hand, all patients suffering from a kidney disease, which is liable to be accompanied by œdema, show a more or less marked diminution in their power of excreting salt.

In the terminal stage of severe cases of nephritis the kidneys may not be able to excrete more than a few decigrammes during a day, so that it is impossible to prescribe a diet sufficiently poor in salt to prevent the retention of a small quantity. In other cases the kidneys can excrete all the salt contained in three pints of milk, but not all that of an ordinary mixed diet. When improvement in the renal condition occurs, the amount of salt which the kidneys can excrete gradually increases, and often finally returns to normal.⁴

Up to now no correspondence has been found between the anatomical changes in the kidneys and the degree in which the power of excreting salt is affected. Moreover the latter is quite independent of the disturbance in the function of excreting other substances such as urea, uric acid, phosphates, methylene-blue and potassium iodide.

Whenever salt is retained in the body, the amount of urine diminishes and the body-weight increases, indicating that water is also being retained. In cases of nephritis this retention of water soon leads to the production of œdema.

It was formerly believed that the sequence of events was opposite to that described. It was believed that the salt was only retained in order to prevent the osmotic pressure of the body-fluids sinking too low owing to the primary retention of water.⁵ If this were true, the percentage of salt in the fluids would either remain normal or become slightly subnormal. It has, however, been found that the percentage of salt in the blood,

⁴ Achard, Widai, Strauss, loc. cit., and many others.

⁵ Marischler, Boas Archiv., vii., 4 and 5, 1902.

œdema fluid, serous effusions and tissues, in cases of Bright's disease, is frequently higher than normal.⁶ Moreover in a few cases retention of salt has been observed at the onset of an attack of acute nephritis before there was any diminution of volume of the urine and before œdema had begun to form, and Halpern⁷ found that loss of salt continued after all œdema had disappeared and the body-weight had become constant.

Some observations of Marie⁸ and of Halpern⁹ indirectly lead to the same conclusion. In the period of diminishing œdema they frequently found that much more salt was lost than corresponded to the loss of fluid as estimated by the diminution in the patients' weight. This must be due to the removal from the body of the excess of salt, the presence of which may barely manifest itself as an abnormally high percentage in the blood or œdema fluids, owing to its being distributed throughout the very large quantity of water which is present in the body. It is impossible to explain these facts in any other way than by supposing that the retention of salt is primary, and that the retention of water, though possibly in part due to the deficient functional activity of the kidneys, is mainly brought about by the regulating mechanism of the organism, which tends to prevent the osmotic pressure of the tissue-fluids rising too high. The tissues suffer when the osmotic pressure of the surrounding fluid differs more than slightly from the normal.¹⁰

Hence when the excretion of salt is deficient, its retention is unaccompanied by that of water until the osmotic pressure has risen to a dangerous height, at which point retention of water in addition becomes necessary.

These conclusions have been confirmed by the observation of a number of cases of unilateral kidney disease, in which no œdema was present, but in which the urine from the diseased kidney obtained by catheterisation of the corresponding ureter contained

⁶ v. Koranyi, *Zt. f. klin. Med.*, xxxiv., 1, 1898; Strauss, *Die chronischen Nierenentzündungen*. Berlin, 1902.

⁷ Salkowski's *Festschrift*, p. 125. Berlin, 1904.

⁸ *Compt. Rend. de la Soc. de Biol.*, 14th Nov., 1903.

⁹ *Loc. cit.*

¹⁰ *Vide p.* 267.

a smaller percentage of salt than that from the normal side.¹¹ The normal kidney is able to make up for the deficiency of the diseased one, so that no retention of salt occurs and consequently no œdema is produced. These observations definitely prove that the capacity of the kidney for excreting salt may be diminished apart from retention of water in the body.

There can thus be little doubt that the retention of sodium chloride occurs in Bright's disease owing to the diminished power of the kidneys to excrete it. The next question to decide is in what way this can give rise to œdema.

As already pointed out, the retention of salt leads to the retention of water, but œdema is not the immediate sequel. Thus at the onset of an attack of acute nephritis diminution in the amount of urine and increase in the body-weight show that retention of water is taking place, although sometimes no obvious œdema appears until two or three days later. Moreover in convalescent patients, who have no longer any œdema, the repeated administration of ten grammes of salt may lead to a temporary increase in weight, which even reached ten kilogrammes in one of Widal's cases, without giving rise to œdema.

Achard,¹² Widal,¹³ and several later writers on the subject believed that the retained salt passed at once into the tissues owing to the supposed power of the blood to keep its composition constant, and that consequently the retained water accumulated exclusively in the tissues even before the œdema was produced. But I have elsewhere¹⁴ shown that, in spite of many statements to the contrary, filtration of a fluid such as blood-plasma, which contains albumin as well as salt, through animal membranes does not result in increased concentration of the salt in the filtrate. Hence an occurrence such as that supposed by Achard and Widal to take place would have to depend on active

¹¹ Casper and Richter, *Functionelle Nierendiagnostik*, Berlin, 1901. Illyés and Kövesi, *Berl. Klin. Woch.*, xxxix, 321, 1902. Luys (*La Séparation de l'Urine des deux reins*, Paris, 1904) obtained similar results by means of the segregator.

¹² *Loc. cit.*

¹³ *Loc. cit.*

¹⁴ *Zeitschr. f. Physiol. Chemie.*, xlviii, 347, 1906.

secretion of salt by the vascular walls. Such an unlikely explanation would need very strong evidence in order to be accepted, and at present it seems much more probable that the retained salt is at first distributed by diffusion from the blood equally through the fluids of the body; when, after further retention, the osmotic pressure of the blood rises to a dangerous point, secondary retention of water occurs. Thus the blood maintains an almost constant percentage of salt by retention of water and not by excretion of salt. The evidence that such an abnormal accumulation of water within the blood-vessels really occurs consists in the diminution which has been observed in the percentage of albumin and hæmoglobin, in the number of red corpuscles in a cubic millimetre and in the specific gravity of the blood, whilst the percentage of salt and the osmotic pressure are slightly increased. Though this condition of the blood, which was first believed to exist by Bright himself and was later more fully examined by Hammerschlag¹⁵ and Diabella and v. Kétly,¹⁶ shows that hydræmia is present, it does not definitely prove the existence of plethora. Up to now no direct measurement of the volume of blood in cases of Bright's disease has been made to settle the question, but in absence of such measurement it is fair to assume that the hydræmia is due to the accumulation of abnormally large quantities of water in the blood-vessels, with the result that a condition of hydræmic plethora develops.

Many years ago it was independently urged by Grainger Stewart¹⁷ and by Bartels¹⁸ that hydræmic plethora was the cause of renal œdema, though they considered that the former was due solely to diminished excretion of water by the kidneys, as the progress and retrogression of the œdema varied inversely with the amount of urine. There is little doubt that this factor does indeed aid in the production of the hydræmic plethora. Thus

¹⁵ *Zeitschr. f. Klin. Med.*, xxi., 475, 1892.

¹⁶ *Deutsche Arch. f. klin. Med.*, lxi., 76, 1898.

¹⁷ *Bright's Disease of the Kidneys.* Edinburgh, 1871.

¹⁸ *Ziemssen's Handb. der spec. Pathol. u. Therapie*, ix., 1, 1877.

it has been found¹⁹ that patients suffering from mild forms of Bright's disease with a tendency to produce œdema, after drinking an extra quantity of water, begin to excrete it after a longer interval than normal and the excretion is prolonged over an unusually long period. In severer cases, accompanied by marked œdema and oliguria, the drinking of water may be followed by little or no increase in the amount of urine, the water being retained and the œdema increased. By testing the reaction of nephritic patients to extra quantities of salt and of water, it is found that the power of the kidneys to excrete either of the two may be affected more or less independently of the other. The fact that the body-fluids generally contain an abnormally high percentage of salt in Bright's disease shows that the diminished power of excreting salt is in most cases present to a greater degree than diminished power of excreting water, though the proportion of the two retained depends of course largely upon how far their supply in the food is restricted.

Cohnheim²⁰ showed that the artificial production of hydræmic plethora by intravenous injection of normal saline solution into animals was followed by a rise in the venous and hence probably in the capillary blood-pressure, in consequence of which there was a great increase in the flow of lymph, and ascites and œdema of the abdominal viscera resulted. But in no case was any subcutaneous œdema produced. Similarly the hydræmic plethora, which results from deficient excretion of salt and water in man, is insufficient by itself to produce œdema, for in cases of calculous anuria, which may last for ten or even more days, during which a very considerable quantity of fluid must accumulate in the body, œdema never occurs.

It is thus clear that, however important hydræmic plethora may be for the production of œdema, it cannot be the sole cause. The second essential factor, which has been completely ignored by the French writers who have insisted on the importance of salt retention, was shown by Cohnheim to be increased

¹⁹ Kövesi and Roth-Schulz, *Berl. klin. Woch.*, xxxvii., 321, 1900; Strauss, *Zeits. f. Klin. Med.*, xlvii., 337, 1902.

²⁰ *Virch. Arch.*, xcvi., 106, 1877.

permeability of the walls of the cutaneous blood-vessels, which he believed to be normally less than that of the vessels of the abdominal viscera, a belief since confirmed by the work of Starling. Cohnheim produced experimentally an increase in the permeability of the cutaneous vascular walls by the local application of irritants and by obstructing the venous circulation so as to impair their nutrition. In these experiments, however, no œdema resulted unless hydræmic plethora was simultaneously produced by injection of saline solution, proving that increased permeability by itself is also insufficient to produce œdema. In Bright's disease Cohnheim believed that the injury to the blood-vessels was brought about by poisons of various origins circulating in the blood. The probability of this was heightened by the experiments of Magnus,²¹ who showed that artificial hydræmic plethora gave rise to generalised œdema if the animal was poisoned by means of arsenic, the toxic properties of which have been shown by Schmiedeberg²² to be due to the injury it inflicts on the capillary walls. The observations of Starling²³ and of Kast,²⁴ who found that the blood serum and œdema fluid of patients suffering from Bright's disease produce a greatly increased flow of lymph when injected into animals, prove that the toxins, which Cohnheim believed on theoretical grounds to be present, actually exist.

Much attention has lately been paid to the possible relation of changes in the tissues themselves to the formation of œdema, and some authors, especially Lazarus-Barlow²⁵ and Bainbridge,²⁶ believe that such changes form the only important factor. According to Lazarus-Barlow, the diminished excretory power of the kidneys in Bright's disease causes the tissues to retain in their lymph spaces the products of their metabolism, which attract water from the blood and thus give rise to œdema. But the latter may occur in Bright's disease in the absence of

²¹ Arch. f. exp. Path. u. Pharm., xlii., 250, 1899.

²² Grundriss der Pharmakologie, p. 408, 1902.

²³ Arris and Gale Lectures, Lancet, May 23rd, 1896.

²⁴ Deutsch. Arch. f. Klin. Med., lxxiii., 562, 1902.

²⁵ British Medical Journal, 1895, i., 631 and 691.

²⁶ Loc. cit.

retention of nitrogen, the excretion of salt and nitrogen being absolutely independent of each other.²⁷ But even if retention of products of metabolism occurred, equilibrium would be maintained by their diffusion into the blood, so that no accumulation in the tissue spaces with consequent rise in osmotic pressure would result. Moreover, according to this theory, the œdema should collect principally in the muscles, including the heart, and not, as is actually the case, in the subcutaneous tissue where metabolism is least active.

It is generally agreed that the distribution of the subcutaneous œdema in Bright's disease depends on the variations in the elasticity of the tissues in different parts of the body. It is possible that the formation of œdema is specially favoured in Bright's disease by the injurious action of the toxins circulating in the body on the elasticity of the subcutaneous tissue. Impaired elasticity would result in an increase in the difference between the intra- and extra-capillary pressure, so that filtration of lymph would be increased and its absorption would be hindered. It seems not improbable that this factor, which has been almost invariably ignored by writers on the subject ever since it was first suggested by Landerer²⁸ more than twenty years ago, may be of considerable importance.

There is no relation between œdema and the retention of other salts than sodium chloride. Thus the excretion of phosphates and sulphates is on the whole parallel with that of nitrogen in cases of nephritis,²⁹ and the latter varies quite independently of the excretion of sodium chloride and the production of œdema. There is also no evidence that potassium or calcium is retained in Bright's disease.

²⁷ Widal and Javal, *Compt. rend. de la soc. de biol.*, 10th Dec., 1903.

²⁸ *Die Gewebespannung*, Leipzig, 1884. Quoted in Krehl's *Pathologische Physiologie*, p. 119, Leipzig, 1904.

²⁹ Fleischer, *Deutsch. Arch. f. klin. Med.*, xxix., 129, 1881.

II.—CARDIAC ŒDEMA.

The interest which has recently been excited in connection with the part played by sodium chloride in the production of œdema has been mainly confined to Bright's disease. But in the second great group of cases in which œdema may occur—cases of cardiac failure—the renal circulation is often deficient, as shown by the presence of albumin and of occasional hyaline casts and red blood-corpuscles in the urine. Hence impairment in the excreting functions of the kidneys might quite conceivably be present. The diminished power of excreting water by the congested kidneys has in fact for many years been held to play an important part in the production of cardiac œdema; but the retention of salt has almost invariably been considered to be secondary to that of water and quite independent of disturbance in the capacity of the kidneys to excrete it.³⁰ Though various French authors³¹ have advised a diet poor in salt for the treatment of cardiac œdema, Strauss³² alone has definitely ascribed the retention of salt in heart disease to the impaired excretory power of the kidneys.

Acting on a suggestion of Prof. Fr. Müller of Munich, I have endeavoured to throw some light on the question by examining how far the kidneys of patients in various stages of heart disease can cope with any extra quantity of salt they may be called upon to excrete. For this purpose the composition of the diet was kept as constant as possible, and on one day during each investigation 10 grms. of sodium chloride were given to the patient. Each day the patient was weighed and the amount of salt in the urine was estimated by Volhard's method. In the first two cases a Kjeldahl nitrogen estimation was also made and the freezing-point of the urine was determined by means of

³⁰ Grassmann, *Zeitschr. f. klin. Med.*, xv., 183.

³¹ Merklen. *Soc. méd. des hôp. de Paris*, 19 juin, 1903; Widal, *loc. cit.*

³² *Loc. cit.*, p. 1.

Beckmann's apparatus. The salt in the fæces was not determined, as numerous observations have shown that the amount present is negligible³³ except in severe cases of diarrhoea, and Halpern³⁴ found that in the salt retention of nephritis none was vicariously excreted by the bowels.

Cases 1 and 2 were investigated in the laboratory of the Second Medical Klinik of Munich, by kind permission of Prof. Müller. I am indebted to Dr. Vickery of the Massachusetts General Hospital for permission to investigate Case 3 and to Dr. Alsberg for permission to do the chemical part of the work in the Laboratory for Physiological Chemistry of Harvard University.

CASE 1.—Joseph K., aged 60, had cardiac failure from myocardial degeneration.

Period I. Ascites and considerable œdema were present and the urine contained a small quantity of albumin. The patient was kept in bed and was given a dry diet poor in salt.

Date. 1905.	Body Weight in Kilo- grams.	Amount of Urine in cc.	Specific Gravity of the Urine.	NaCl per cent.	NaCl in Grms.	N. per cent.	N. in Grms.	Freez- ing Point Depres- sion (Δ)	
Oct. 8	86.5	480	1.018	0.854	4.10	1.22	5.84	—	Average NaCl 4.65 gms.
" 10	86.5	652	1.017	0.889	5.80	0.99	6.34	—	
" 11	86.6	652	1.012	0.584	4.04	0.69	4.85	—	Average N. 5.52 gms.
" 13	86.6	585	1.016	0.796	4.65	0.86	5.04	1.17	

The figures for the body-weight show that the œdema was not increasing. The small quantity of urine and salt excreted must therefore have been due to the small quantity of water and salt in the diet.

³³ Schmidt and Strasburger, *Die Fæces des Menschen*, 242, 2nd edition, 1905.

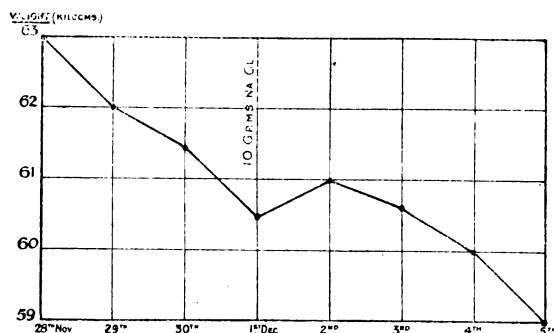
³⁴ Loc. cit.

Period II. During the interval of forty-five days between periods I. and II. digitalis and theocin had been given and copious diuresis had resulted. The weight of the patient had diminished by 23.5 kilogrammes, this being probably entirely due to loss of cedema. During this period of investigation only the digitalis was continued, and the diet was somewhat less restricted than in period I. On December 1st 10 grms. of sodium chloride were given.

Date. 1905.	Body Weight in Kilo- grams.	Amount of Urine in cc.	S. G.	NaCl per cent.	NaCl in Grms.	N. per cent.	N. in Grms.	Δ	
Nov. 28	63.0	2485	1.012	0.593	14.74	0.606	15.07	0.87	Average NaCl 14.56 grms. Average N. 13.95 grms. Aver. daily loss of wght. 750 grms.
" 29	62.0	3100	1.008	0.480	14.87	0.453	14.05	0.70	
" 30	61.5	2730	1.009	0.515	14.05	0.466	12.73	0.78	
Dec. 1	60.5	2770	1.010	0.503	13.94	0.534	14.79	0.79	10 grms. NaCl given.
" 2	61.0	2700	1.012	0.562	15.16	0.610	16.46	0.83	Average NaCl 13.16 grms. Average N. 14.70 grms.
" 3	60.6	2410	1.010	0.526	12.69	0.565	13.50	0.88	
" 4	—	2260	1.010	0.468	10.58	0.603	13.63	0.79	
" 5	59.0	2760	1.010	0.515	14.21	0.551	15.20	0.81	

In spite of the fact that good diuresis was present, the average amount of salt excreted during the four days following the administration of the 10 additional grms. was no greater than that of the three preceding days. Hence all the 10 grms. must have been retained in the body. Up to the time that the salt was given the cedema had been constantly diminishing, the average daily loss in weight during the four preceding days having been as much as 830 grms. as compared with a daily average of 500 grms. for the previous forty-five days. But the day following the administration of the salt the patient's weight was actually 500 grms. more than on the day of administration. If this is added to the 830 grms., which would have probably represented the day's loss in weight if no salt had been taken, it is seen that about 1330 grms. of water were retained as a

consequence of giving the 10 grms. of salt. Thus the proportion of salt to water retained corresponds to a 0·8 per cent. solution of the former, a strength only slightly lower than that of normal saline solution. The accompanying chart shows graphically how the weight was affected by the administration of the salt.



Period III. At the end of period II. the œdema had almost completely disappeared. During the following thirty-six days the last traces vanished and the patient's general condition greatly improved, but a trace of albumin was still present in the urine. A small dose of digitalis was still given each day. 10 grins. of common salt were given on January 14th.

Date. 1906.	Body Weight in Kilo- grams.	Amount of Urine in cc.	S. G.	NaCl per cent.	NaCl in Grms.	N. per cent.	N. in Grms.	Δ	
Jan. 10	58·5	2100	1·010	0·503	10·56	0·660	13·86	0·84	Average NaCl 12·76 gms.
" 11	58·5	3400	1·010	0·445	15·13	0·593	20·16	0·77	
" 12	58·0	2800	1·011	0·515	14·42	0·691	19·35	0·84	Average N. 17·56 gms.
" 13	58·0	2600	1·010	0·421	10·95	0·649	16·87	0·85	
" 14	58·5	2400	1·010	0·374	8·98	0·632	15·17	0·74	10 gms. NaCl given.
" 15	59·6	2640	1·010	0·351	9·23	0·638	18·64	0·79	Average NaCl 6·84 gms.
" 16	60·0	2410	1·010	0·304	7·33	0·742	17·88	0·85	
" 17	60·0	2400	1·008	0·246	5·90	0·939	22·54	0·98	Average N. 16·25 gms.
" 18	61·0	1620	1·012	0·304	4·92	0·590	9·56	0·75	
" 19	61·4	1710	1·013	0·398	6·81	0·843	14·41	0·96	

In spite of the marked improvement in the condition of the patient all the 10 grms. of salt given on January 16th were retained in the body. But the average amount of salt in the day's urine was actually 5.92 grms. less after the administration of the salt than before it. Hence not only were the 10 grms. of salt retained but they appear to have caused the retention of an additional 29.6 grms. of salt from the food during the subsequent five days. As a consequence the œdema temporarily returned and the body-weight increased by 3,400 grms. in this period. The retention of water and salt was in the proportion of a 1.17 per cent. solution. Now a 0.9 per cent. solution of sodium chloride is isotonic with the human plasma, so that a rather smaller quantity of water appears to have been retained than exactly corresponds to the amount of salt retained. This is also true for the retention in period II., if allowance be made for the fact that, as in period III., the average percentage of salt was not only not greater after the administration of 10 grms. of salt but was actually less than before. If this extra amount of salt be added to the 10 grms. the amount of salt and water retained in period II. also approximately corresponds to a 1.17 per cent. solution. This can only be explained by assuming that, as in the case of Bright's disease, only sufficient water is retained to prevent the osmotic pressure of the body-fluids rising to a point which would be injurious to the tissues. The addition of $3\frac{1}{2}$ litres of a 1.17 per cent. solution of salt to all the fluid contained in the body would only raise its osmotic pressure to a very slight extent.

CASE 2.—Martha R., aged 33, had fully compensated mitral incompetence. She had previously suffered from slight œdema and other signs of heart failure, but appeared now to be well in every way, her urine being quite normal. During the investigation she was kept in bed, but received no medicine. 10 grms. of salt were given on October 14th.

Date. 1905.	Body Weight in Kilograms.	Amount of Urine in cc.	S. G.	NaCl per cent.	NaCl in grams.	N. per cent.	N. in grams.	Freezing Point Depression.	
October 8 ...	53.0	1375	1.016	0.877	12.07	0.864	11.88	1.37	Aver. amount of Urine 1584 cc.
" 9 ...	—	1820	1.013	0.725	13.20	0.616	11.82	0.98	
" 10 ...	—	1780	1.014	0.760	13.54	0.690	12.28	—	
" 11 ...	52.5	1675	1.017	0.877	14.65	0.707	11.80	—	Aver. NaCl 12.60 grms.
" 12 ...	52.5	1075	1.021	0.842	9.06	0.945	10.16	1.37	
" 13 ...	52.0	1480	1.019	0.877	13.09	0.778	11.51	1.35	Aver. N. 11.58 grms.
" 14 ...	52.5	915	1.022	1.065	9.74	1.168	16.90	1.71	
" 15 ...	53	1300	1.021	1.228	15.97	1.012	13.15	1.70	10 grms. NaCl given. Excess NaCl over aver. 3.97 Excess N. over aver. 1.57
" 16 ...	52.5	1615	1.017	0.948	15.50	0.809	13.08	1.36	
" 17 ...	—	1560	1.020	1.100	17.16	1.017	15.86	1.60	
" 18 ...	52.7	1320	1.020	0.983	12.97	1.057	13.95	1.51	
" 19 ...	—	1370	1.016	0.948	12.98	0.767	10.59	—	
							11.59	—	8.74

Taking the average of the salt excreted during the six days which preceded that on which the 10 grms. of salt were given as the normal, it is seen that on the day itself none of the excess was excreted, but on the three following days 3.37 grms., 2.90 grms., and 4.56 grms. respectively more than the normal average were excreted. These amount together to 10.83 grms., so that it is clear that the kidneys required four days, including that on which the salt was given, instead of the normal period which varies between twenty-four and forty-eight hours, in order to completely excrete the 10 grms. given on October 14th. This was probably due to the fact that the kidneys were unable to excrete more than 17 grms. of salt on a single day, though the normal kidneys can always excrete more than 20 grms.⁸⁵ During the day on which the 10 grms. of salt were taken 619 c.c. less urine were passed than the average amount of the previous six days, and on the following day 234 c.c. less. This diminution was probably due to retention of water secondary to the temporary retention of salt, a conclusion which is supported by the fact that the body-weight increased during the same two days by 1,000 grms., an amount corresponding fairly accurately with the deficiency in the quantity of urine. In spite of this retention of fluid, no obvious œdema resulted, probably owing to the improved condition of the vessel walls resulting from the restoration of the circulation and to the absence of the mechanical factors present during failure of compensation.

CASE 3.—Maurice L., aged 8, had mitral regurgitation due to acute rheumatism. The condition was well compensated and the urine normal, but the patient had had slight œdema and pleural effusion, which had disappeared a week before the investigation began. During the investigation he received small doses of digitalis. 4 grms. of NaCl were given at 7 p.m. on July 31st, and 4 grms. at 7 a.m. on Aug. 1st.

⁸⁵ Thus in case 3, though the patient was only eight years old, an addition of 8 grms. of salt to the diet led to the excretion in one day of 21 grms.

Date. 1906.	Weight at 8.30 a.m. in kilograms.	Amount of urine in c.c. from 7 a.m. to 7 a.m.	Percentage sod. chloride.	Total sod. chloride in grms.	At midday.	
					Hæmo- globin per cent.	Red corpus- cles per c.mm.
July 28	23.0	1570	0.75	11.80	85	6,500,000
29	—	1800	0.49	8.82	—	—
30	22.9	1845	0.64	11.80	—	—
31	22.9	1290	0.675	8.71	88	6,500,000
		Average 1626		Average 10.28		
Aug. 1	23.5	1110	0.52	5.80	80	5,820,000
2	23.1	2175	0.975	21.10	90	6,700,000
3	23.0	1320	0.675	8.91	92	6,700,000
4	23.0	1690	0.55	9.29	—	—

In this case, as in cases 1 and 2, the immediate effect of the administration of the salt was actually a diminution in the amount excreted. Thus on August 1st 4.48 grms. less salt were excreted than the average amount for the previous four days. On the following day an excess of 10.82 grms. were excreted, so that all the additional quantity of salt was excreted within a period of thirty-six hours. This, taken with the fact that 21.1 grms. of salt were excreted during a single day (August 2nd), shows that the capacity of the kidneys to excrete salt was normal. The increase in body-weight on August 1st was about 500 grms. ; on August 1st about 500 c.c. less urine were excreted than the average for the four days preceding the administration of the salt, and on August 2nd about 500 c.c. more. Hence about 500 c.c. of water were retained in the body with the 10 or 12 grms. of salt, showing that retention of water only begins after the osmotic pressure of the body-fluids has risen somewhat above normal. The ten per cent. diminution in the hæmoglobin percentage and in the red corpuscle count of the blood on August 1st shows that the temporary retention of water led to a condition of hydræmic plethora, which disappeared on the following day with the excretion of the excess of water.

Period II. of case 1 shows that in cardiac œdema the power of the kidneys to excrete salt is impaired; period III. of the same case and case 2 show that this impairment may still be present when the condition of the circulation has greatly improved, and even when, as in case 2, the urine is quite normal. Finally case 3 shows that complete restoration of this function of the kidneys can occur.

In all three cases less salt was excreted on the day of administering the extra quantity than on the previous days, and in case 1 this diminution continued for some time after; this shows that excessive quantities of salt in the food have at any rate a temporary inhibitory effect on the power of the kidneys to excrete it.

These investigations further show that the retention of salt due to impaired renal circulation gives rise to a secondary retention of water. In case 3 the examination of the blood showed that the temporary retention of water gave rise to a condition of hydræmic plethora. But in cases of cardiac failure, in which salt contained in the ordinary diet is retained, the evidence for the presence of hydræmic plethora, as in Bright's disease, is indirect. It is inferred from the hydræmia which has been frequently observed at the onset of cardiac œdema.³⁶ In three severe cases, however, Kraus³⁷ failed to find any evidence of its occurrence, so that he concludes that it plays no part in the production of the œdema of heart failure. But his observations can be otherwise explained. Thus plethora may occur without hydræmia; for Lorrain Smith³⁸ has shown by actual measurement that the volume of the blood in chlorosis is greatly increased, although its specific gravity is generally normal,³⁹ and a normal number of red corpuscles may be present. Presumably in chlorosis there is an increased supply of the nitrogenous constituents of the blood to compensate for the dilution due to the increase in water, and

³⁶ Stintzing and Gumprecht, *Deutsch. Arch. f. klin. Med.*, liii., 465, 1894; and many others.

³⁷ *Therapie der Gegenwart*, July, 1903.

³⁸ *Trans. of the Pathol. Soc.*, 1900.

³⁹ Strauss in v. Noorden's *Pathologie des Stoffwechsels*, Bd. I., 935, 2nd edition, 1906.

there is no reason why a similar change should not occur in cases of plethora due to heart disease. In the early stages this would not yet have had time to develop, but it would be present in such cases as those of Kraus in which the heart failure appears to have been of long standing.

The plethora due to deficient renal activity causes a rise in capillary pressure and leads to increased filtration of lymph. This is further helped by the increased permeability of the vessel-walls due to impaired nutrition caused by the venous and watery state of the blood and the slow circulation.

It is still doubtful what part changes in the capillary and venous blood-pressure due to other causes than hydræmic plethora play in the formation of cardiac œdema. Most probably the deficient power of the heart gives rise to an increased venous and capillary pressure. The latter increased by the hydræmic plethora give rise to excess of lymph formation, and the former diminishes its absorption by the venules. Further, as Starling⁴⁰ has pointed out, the considerable rise of pressure in the veins near the heart obstructs the outflow of lymph from the thoracic duct and thus further increases the œdema.

Possibly tissue changes, especially diminished elasticity of the connective tissue brought about by the same causes which give rise to the increased capillary permeability, assist in the production of the œdema of heart disease.

3.—CACHECTIC ŒDEMA.

The third important group of diseases in which œdema occurs is that of the anæmias and various cachectic conditions. There is at present no evidence to show that retention of salt has any connection with the production of œdema in these cases, so that they need not be further discussed here.

4.—“ IDIOPATHIC ” ŒDEMA.

There is a very rare group of cases in which œdema occurs with no-obvious organic disease and in the formation of which salt probably plays an important rôle. The only case of this sort

⁴⁰ Loc. cit.

occurring in adults, which has been carefully investigated, was recorded by Dr. Bryant.⁴¹ A man with apparently perfectly healthy heart and kidneys suffered from œdema of the legs. The normal daily amount of salt taken with the food averages about 15 grms., and a healthy man can excrete in twenty-four hours as much as 20 grms. in excess of this quantity. But Dr. Bryant's patient was in the habit of taking from 20 to 40 grms. every day, so that retention of salt naturally ensued. This must have led to increasing hydræmic plethora, which apparently finally reached such a degree that the power of the lymphatics to carry away the excess of lymph became inadequate and œdema resulted. Probably, however, the hydræmic condition of the blood also increased the permeability of the vessel-walls by diminishing their nutrition, as plethora alone is probably incapable of giving rise to œdema. The œdema disappeared rapidly on diminishing the quantity of salt taken with the food.

There is a rare condition occurring in infants, known as "idiopathic" œdema, in which the kidneys are apparently quite normal. Infants suffering from this form of œdema have been found to have been fed on patent foods rich in salt, to which moreover extra salt has often been added; a rapid cure always results on returning to a purely milk diet. In infants it is probable that the power of excreting salt is not highly developed, as they are normally only required to deal with the very small quantity present in fresh milk. Excessive salt in the food will thus readily result in retention in the blood, and this must lead to hydræmic plethora. The capillary vessels of new-born infants are presumably more delicate than those of adults, and this is particularly the case in infants with "idiopathic" œdema, as they frequently suffer from diarrhœa and are more or less ill-nourished. Hence it is not improbable that a condition of over-permeability of the vascular walls coexists with the hydræmic plethora and helps in the production of œdema.

In connection with these cases of salt retention in absence of kidney disease, the observations of Widai and Javal⁴² on the

⁴¹ Practitioner, lxxv., 169, 1905.

⁴² Compt. rend. de la soc. de biol., 12 mars, 1904.

variations produced in the quantity of water in the body by changes in the diet in normal men are of interest. On changing from a full mixed diet containing from 15 to 20 grms. of salt a day to a diet containing less than 1 grm., more salt is at first excreted than is taken in the food. When in three or four days 10 to 12 grms. of salt have been lost, equilibrium is re-established. Corresponding to the loss of sodium chloride there is a loss in the body-weight, which may be as great as two kilogrammes. This must be due to loss of water, as it is much greater than can be explained by the very slight loss of tissue proteid which sometimes occurs simultaneously. On subsequently returning to a normal diet, salt and water are retained until after three days chloride equilibrium on a higher plane is once more established. These results have been fully confirmed by Halpern,⁴³ who further showed that the increased weight with the salt-rich diet was unaccompanied by any changes in the percentage of salt in the blood, but that hydræmia was present as shown by a diminution in the percentage of the total solids.

TREATMENT.

The importance of the retention of sodium chloride in the production of œdema is not merely of theoretical interest. By the application of the facts brought to light by recent research on the subject it has been possible to explain the working of recognized methods of treatment—treatment which was formerly to a large extent empirical—and also to modify them favourably in various directions.

Diet.—It is generally agreed that the diet in cases of Bright's disease is of supreme importance. It is also agreed that the diet must be one which gives the kidneys as little work to do as possible and contains a minimum of substances which may irritate the renal epithelium. For these reasons milk alone is almost universally considered to be the proper diet in cases of acute and subacute nephritis. In chronic parenchymatous nephritis a milk diet is generally given, at any rate in the early stages, and so long as œdema is present it is usual to keep the

⁴³ Loc. cit.

diet very simple. It will, however, be acknowledged that the results of such a régime in cases of chronic Bright's disease are far from satisfactory, and even in acute nephritis they are frequently disappointing. It is obvious that the restoration of the kidney cells to a condition approaching as nearly as possible to the normal largely depends on their receiving an adequate supply of nutrition. Not only do the injured cells, in which microscopical examination often reveals signs of active regeneration, require sufficient food, but all the tissues and organs of the body, and especially the blood vessels and perhaps the connective tissues, the injury to which aids in the production of œdema, should be maintained in as healthy a condition as possible.

It is, however, notorious that a milk diet is a starvation diet. In the attempt to protect the kidney cells from further injury they are deprived of the nourishment which is essential for their recovery, and at the same time the rest of the body suffers, as shown by the wasted muscles and scanty fatty tissue, which are so frequently present in Bright's disease, though often masked by the abundance of the œdema.

This difficulty has frequently been recognised; but the danger to the kidneys of a more liberal supply of food has been considered to outweigh the defective nutrition which accompanies a milk diet. The main ground for this belief is the favourable influence of a milk diet on œdema, the increase or diminution of which is often assumed to give an indication of the condition of the kidneys. Thus it is generally held that the increased œdema which is often the immediate sequel of a change from a milk to a more liberal diet is a sign that the kidneys are being injuriously affected.

This view is, however, erroneous, and the increase in the œdema is due solely to the additional quantity of salt which always accompanies an increase in the allowance of food. Thus it is only in cases in which the power of excreting salt is diminished that a liberal diet is feared. Nobody to-day thinks of restricting a patient with granular kidney to milk, although the renal epithelium is frequently more seriously injured than in mild cases of

acute and chronic Bright's disease. In such cases a mixed diet can be given with impunity, as the kidneys have not lost their power of excreting salt in normal quantities.

While three pints of milk contain only $2\frac{1}{2}$ grms. of salt, an ordinary mixed diet contains 15 grms. In a patient whose diseased kidneys are capable of excreting 6 grms. of salt in a day, there would be no retention of salt on a milk diet, but 9 grms. on a full diet. Consequently there would be no increase of œdema with the milk, but about a litre of fluid would daily be retained in the body with the full diet. The difference might be even more striking, as with the milk diet there might be some salt in addition to that of the food excreted, so that an actual diminution of œdema might occur. That this is not always the case is due to the fact that in severe nephritis the restriction of salt in the food is sometimes followed by a diminution in the amount excreted, so that, although the formation of œdema is checked, it does not at once begin to disappear.

A carefully chosen mixed diet, apart from the addition of salt in cooking and while being eaten, contains about 1 gm. less salt than three pints of milk. Such a diet would therefore be even more efficacious than a milk diet in preventing the increase of œdema and causing the disappearance of that already present. Thus Widal and Javal report the case of a patient with chronic parenchymatous nephritis, whose kidneys were able to excrete only 2 grms. of salt, so that on a milk diet there was a small daily retention and consequently a slow but constant increase in the œdema. On changing to a diet of meat, bread and potatoes, all prepared without salt, the œdema disappeared, as only about 1 gm. of salt was daily ingested. On returning again to a milk diet the œdema came back, but disappeared once more with the salt-free meat, bread and potato diet.

A mixed diet as poor as possible in salt has the additional advantage of maintaining the tissues in a state of good nutrition and of permitting the slight restriction of fluid sometimes advisable on account of the diminished capacity of the kidneys to excrete water. The practice of giving large quantities of fluid in cases of acute nephritis with the object of washing away the

casts, blood, and epithelial cells which obstruct the tubules is probably a mistaken one, as even if the power of excreting water is but little impaired, the additional work thrown upon the kidneys in order to cope with the excessive supply of water must be injurious to them. In convalescence, however, when the excretory function of the kidneys has returned to normal, an abundant supply of water may be usefully given without fear of doing any harm.

Another argument often employed in favour of a milk diet in Bright's disease is the increase in albuminuria which generally follows a change to a more varied diet, as it is held that this indicates a deterioration in the condition of the kidneys, although the albuminuria in itself is not considered to be dangerous. But von Noorden⁴⁴ believes that the increase is due to the change rather than to the increase in the diet, as he has observed that it not infrequently occurs when the change consists in a return to a simple diet from a more liberal one. Moreover, Widai and Javal⁴⁵ found that in many cases the degree of albuminuria in Bright's disease bears a close relation to retention of salt, as with a mixed diet, containing meat but very little salt, a nephritic patient often excretes no more albumin than on a purely milk diet, and, if the mixed diet be of such a nature that it contains even less salt than the milk, its use is accompanied by an actual diminution in the albuminuria. Vaquez and Laubry⁴⁶ have made similar observations in cases of cardiac oedema associated with albuminuria. Some experiments of Castaigne and Rathery⁴⁷ seem to show that the increased albuminuria which is often produced by excess of salt in the food is due to the directly injurious action of salt on the kidneys when its concentration is above a certain point. Thus a solution of sodium chloride with a freezing point below 0.78° produced degenerative changes in renal cells *in vitro*. Moreover Achard and Paiseau⁴⁸

⁴⁴ Nephritis, p. 24, 1903.

⁴⁵ Compt. rend. de la soc. de biologie, 16 juillet, 1904. Vide also Miller, Trans. of the Assoc. of Amer. Physicians, xx., 435, 1905.

⁴⁶ Bull. de la soc. méd. des hôp. de Paris, 13 nov., 1903.

⁴⁷ Quoted by Achard and Paiseau.

⁴⁸ Compt. rend. de la soc. de biologie, 26 mars, 1905.

observed similar anatomical changes in the kidneys of animals after injection of hypertonic salt solution.

It has been suggested that a diet containing less salt than three pints of milk is dangerous, as a certain daily minimum is necessary for the normal organism. According to Bunge⁴⁹ only 1 or 2 grms. of extra salt are required with a vegetable diet, and with a meat diet it is unnecessary to make any addition to that already present. Castaigne and Rathery⁵⁰ have found that a mixed diet with no salt added to it produces albuminuria in healthy animals and men, and a hypotonic saline solution has the same action as a hypertonic solution on kidney cells *in vitro*. But in Bright's disease the salt-poor diet may actually cause albuminuria to diminish; this is due to the fact that there is excess of salt already present in the blood, so that on diminishing the supply to a minimum, the percentage does not fall below normal as it would in people with healthy kidneys.

But it might be suggested that a mixed diet poor in salt, though actually more favourable than a milk diet in causing the œdema and albuminuria of Bright's disease to disappear, might yet, by giving the kidneys too much to do, have an unfavourable effect, which does not manifest itself in such obvious ways as in the production of œdema and albuminuria. But in practice no ill results have followed the more liberal diet, and it is not difficult to arrange one which gives the kidneys even less work to do than that usually employed.

During the first two or three days in the most acute forms of nephritis associated with partial or complete suppression of urine, Rose Bradford⁵¹ advises complete starvation. Such treatment, however, cannot fulfil the purpose for which it is prescribed, as in the early stages of starvation in adults from 8 to 15 grms. of nitrogen are daily excreted by the kidneys, though on a diet of 1½ litres of milk the urine contains only 7 grms.⁵² But it is possible to give the body much more nourishment than that

⁴⁹ *Lehrbuch der Physiologie des Menschen*, ii., 136, 1905.

⁵⁰ *Loc. cit.*

⁵¹ *Practitioner*, lxxvi., 483, 1906.

⁵² *Landergren, Skand. Arch. Phys.*, xiv., 112, 1903. Quoted in von Noorden's *Pathologie des Stoffwechsels* I., 314. New edition, 1906.

contained in $1\frac{1}{2}$ litres of milk without increasing the amount of nitrogen to be excreted, and at the same time to make a diminution in the supply of fluid possible if this should be considered necessary. Various diets containing no more proteid than $1\frac{1}{2}$ pints of milk were found by Chittenden⁵³ in actual metabolism experiments to be sufficient to maintain nitrogenous equilibrium whilst yielding an energy-value of over 2000 calories. Such diets, which if prepared without salt can be safely given in the severest cases of acute nephritis, can be modelled from the following example:—250 grms. of bread, 250 grms. of potatoes, 50 grms. of fresh-water fish⁵⁴ or chicken, 500 cc. of milk, 50 grms. of sugar, and 60 grms. of butter. Bread baked without salt tends to dry rapidly, so part of it may preferably be taken as bread and milk or in pudding, in both of which the addition of sugar makes the absence of salt less unpleasant. Oatmeal porridge and semolina or rice puddings may be used to replace some of the bread or potatoes, and the fish and chicken may be replaced by eggs or even by meat. If cream does not cause nausea, its high energy value makes it a valuable addition to the diet.

In subacute and chronic nephritis associated with œdema the limitation of proteid is less often necessary than with acute nephritis. As complete metabolism researches alone can show in a direct manner whether the kidneys are excreting as much nitrogen as is taken in the food, it is in practice useful to have some direct evidence that nitrogen retention is taking place. Though uræmia is certainly not due directly to the retention of urinary constituents, it is almost always associated, as Strauss⁵⁵ has shown, with the presence of excess of nitrogen in the blood. This appears at first difficult to reconcile with the observations of Butler and French,⁵⁶ who found in a case of parenchymatous nephritis that in a period of uræmia more nitrogen was excreted

⁵³ *Physiological Economy in Nutrition*, New York, 1904.

⁵⁴ Salt-water fish, with the possible exception of cod, contain too much salt to be a suitable food for œdematous patients.

⁵⁵ *Die chronischen Nierenentzündungen*. Berlin, 1902.

⁵⁶ *Guy's Hospital Reports*, lvi., 49, 1902.

than was taken in the food, though previously there had been some nitrogenous retention. Possibly, however, the onset of uræmia was due to the preceding retention of nitrogen, and the increased excretion during the attack was caused by increased breaking down of tissue-proteid, which Von Noorden⁵⁷ has shown may occur in uræmia.

There is no doubt that the high blood-pressure of nephritis, which is well known to be harmful in its effects on the circulatory system, is directly or indirectly associated with retention of nitrogen. Thus a case of chronic Bright's disease in Müller's clinic had a systolic blood-pressure of 190 mm. when on a full diet, but this fell to 140 mm. when a change to a farinaceous diet was made. High blood-pressure or symptoms pointing to the onset of uræmia⁵⁸ are thus the most valuable indications for the reduction in the nitrogen of the food. But the simplification of the diet may owe some of its favourable influence in controlling high blood-pressure and mild uræmia to the diminution in the salt supply which it involves. Thus Widal⁵⁹ and Miller⁶⁰ observed that retention of salt when excess was given in the diet often led to uræmic symptoms. This at first appears to confirm the older theory of Bohne⁶¹ of a causal connection between sodium chloride retention and uræmia. More extended observations, however, have shown that the connection is only an occasional one, due probably to the retention of water secondary to the retention of salt; for diminution in the quantity of the often already scanty urine may cause the incomplete excretion of the nitrogenous or toxic substances concerned in the production of uræmia. This explanation seems more probable than that given by Widal and Miller, who suggest that the uræmia is due to œdema of the brain following the retention of salt and water, for it is very doubtful whether this pathological condition has ever any relation to uræmia.

⁵⁷ *Pathologie des Stoffwechsels*, vol. i., p. 971, 1906.

⁵⁸ A sudden rise in blood-pressure is probably one of the most certain warnings of the onset of uræmia.

⁵⁹ *Loc. cit.*

⁶⁰ *Loc. cit.*

⁶¹ *Forts. der Med.* xv., No. 4, 1897.

The observations of Ambard and Beaujard⁶² and of Laufer⁶³ have shown that some relation exists between salt retention and blood-pressure. At the onset of salt retention the pressure rises and may continue to be high until the maximum retention is reached. So long as considerable retention is present the blood-pressure may remain raised, though it is often not above normal. When the excess of chlorides begins to be excreted there is generally a temporary rise of blood-pressure which may be followed by a fall. Laufer, who, unlike most French writers, believes that the retention of salt occurs within the blood-vessels, thinks the initial rise of blood-pressure is due to the hydræmic plethora which occurs, and that with the passage of fluid into the tissues and diminution in the plethora the pressure is likely to fall again. The onset of a diminution in the amount of œdema is accompanied by a rise of pressure owing to the plethora produced by the passage of large quantities of fluid from the tissues into the blood-vessels. This explanation appears to be more probable than a direct action of the salt on the blood-vessels.

In a disease such as chronic parenchymatous nephritis, which may last for many months, it is important that the diet should not only fulfil the conditions already specified, but that it should be prepared in as pleasant a way as possible and should present sufficient variety to keep the patient from losing his appetite. Owing to the necessity of excluding salt, this is only possible by skilful preparation of the food with such substances as fresh butter, sugar, lemon juice and vinegar. Vinegar has often been supposed to be injurious to the kidneys, but as it is completely oxidised in the body it cannot possibly do any harm. It is very desirable that the supposed irritant action on the kidneys of the numerous condiments, spices, vegetables and meat extracts, which, on quite insufficient grounds, are generally avoided in nephritis, should be further investigated, for if found to be harmless they would form a valuable addition to the means of

⁶² Arch. gén. de méd. No. 9, 1904.

⁶³ Compt. rend. de la soc. de biol., jan. 1904.

rendering a salt-free diet palatable.⁶⁴ Until more is known of them, however, it is safest to exclude them from the dietary. There is, however, no doubt at all that alcohol is harmful to the kidneys, so that its use should be rigorously excluded, unless small quantities of weak wine are considered necessary in order to promote the appetite in chronic cases.

In presence of gastro-intestinal disturbances the diet must of course be modified, but it has been found in practice that nephritic patients, unless actually uræmic, can generally take such a diet as described without suffering from indigestion.

The value of a milk diet in cases of cardiac œdema depends as in renal œdema on its poverty in salt. A similar diet to that advised for Bright's disease is therefore of great service, but the power of excreting nitrogen being normal except in the last stages of heart failure, there is no need to limit the amount of proteid. This is fortunate, as it makes it possible to diminish the amount of other food-stuffs in the diet, for excess of carbohydrate is particularly liable in heart failure to give rise to flatulence, which may seriously interfere with cardiac efficiency, and Grassmann⁶⁵ has shown that the absorption of fat is in such cases somewhat impaired, though that of proteid and carbohydrate remains normal.

Corresponding with the greater importance of mechanical factors in the œdema of heart failure than in that of Bright's disease, it is found that a salt-free diet has generally a less marked effect in causing the disappearance of the former, though it is a powerful aid in preventing its increase. Moreover, when the œdema has almost disappeared as a result of treatment, an ordinary full diet often causes its rapid return, which is prevented by excluding salt from the same diet.

When the œdema has disappeared the amount of salt allowed may be slowly increased in both nephritic and cardiac cases, but

⁶⁴ The belief in the irritant action of meat extracts owes its origin mainly to the considerable œdema which may follow its administration. The œdema, however, is probably due to the very large proportion of salt contained in the extracts as usually prepared.

⁶⁵ *Zt. klin. Med.* XV., 183, 1888,

it is well to weigh the patient at regular intervals, so as to be able by a reduction in the amount of salt in the diet to forestall the onset of œdema, when a sudden increase in weight gives warning that retention of water is occurring, although the production of hydræmic plethora may still be unaccompanied by œdema. In some cases of nephritis it is necessary to limit the amount of salt in the food for several months or even permanently, and case 2 described above shows that even in cases of cardiac disease with apparently perfect compensation the power of excreting salt may be somewhat impaired.

Diuretics.—A knowledge of the relation of retention of salt to the production of œdema gives other indications for treatment in addition to diet. It is found that certain diuretics, the most important of which are caffein and its derivatives (theocin and diuretin), increase the percentage of salt in the urine as well as the amount of water excreted. Others, such as digitalis, which act indirectly by improving the renal circulation owing to their effect on the heart, do not influence the percentage of salt, or the diuresis may even be associated with a fall in the percentage, as can be seen by comparing the analyses of urine in period II. with those of period I. in case 1. This explains the fact that caffein, diuretin and theocin, in proportion to the amount of diuresis they produce, diminish œdema to a greater extent than any other drugs. As, however, they directly stimulate the kidney cells, they are ineffective in many cases of Bright's disease in which the cells are too much injured to be able to respond adequately. Even in cases in which they act, their employment is open to criticism, as their irritant action may perhaps be injurious to the cells of the kidneys. Hence, instead of throwing more work upon the diseased kidneys by the use of renal diuretics, it is more rational to give a diet which makes as small a demand upon them as possible, and, by increasing the activity of other organs, to attempt to relieve the kidneys of some of the work they would otherwise have to do. There is, however, no reason why diuretics such as digitalis, which only act indirectly, should not be used, though they cannot be

expected to have any effect except in cases in which the renal incapacity is complicated by cardiac weakness.

But in cardiac œdema good results are almost always obtained by the use of caffein and its derivatives. Theocin is frequently even more valuable than caffein, as the initial dilatation of the blood-vessels, which it produces in addition to its direct action on the kidney cells, is not followed by constriction, as is the case with caffein.⁶⁶ Theocin deserves to be much more widely employed than it has been up to now in England, as the œdema in a case of heart failure, which does not disappear though held in check by a salt-free diet and the administration of digitalis, often rapidly clears up if theocin is also given for a few days. Potassium acetate has a similar but much weaker influence on the percentage of salt in the urine, and it can be profitably given to help to maintain the diuresis initiated by digitalis and theocin when the effect of the latter drug is diminishing, as frequently occurs after three or four days' use.

Diaphoresis.—The production of diaphoresis has long been one of the chief methods employed in treating nephritis. So far as œdema is concerned, this must be most useful in those cases in which the power of the kidneys to excrete water is much affected; when this is insignificant in comparison with the loss of power to excrete salt the diaphoresis will be of less value, owing to the small amount of salt contained in sweat. A litre contains about $3\frac{1}{2}$ grms.,⁶⁷ so that of every litre of fluid lost by sweating about 600 c.c. will be immediately replaced by retention of water taken by the mouth. But when the renal excreting power for salt is greatly impaired, the comparatively small quantity which is excreted in the sweat called forth by electric light baths may yet materially help a diet poor in salt in getting rid of œdema. Thus in a case of chronic parenchymatous nephritis with very severe œdema, under the care of Dr. J. H. Pratt of the Massachusetts General Hospital, who examined the chloride excretion with me, no improvement had taken place for

⁶⁶ Caffein, however, has the advantage of being a more powerful cardiac stimulant than theocin or diuretin.

⁶⁷ Brieger, *Deutsch. med. Woch.* xxix., 421, 1903.

several months on a farinaceous diet. On changing the diet to one rather more abundant but containing only a minimum of salt, an immediate improvement was observed. This became still more marked on giving electric light baths of half an hour's duration every second or third day. By weighing the patient before and after each bath it was found that in six baths taken in a period of eighteen days she lost 3·7 kilogrammes of sweat.⁶⁸ Taking the percentage of salt in sweat as 0·35, it follows that she lost about 12 grms. by the skin, and in the same period she lost 27 grms. of salt by the urine, so that nearly one-third of the total amount lost by the body was excreted by the sweat. Hence of the 5·6 kilogrammes of œdema fluid, which the diminution in her weight showed that she had lost in the eighteen days, nearly a third was due to the diaphoresis. Thus, though 2·3 kilogrammes of sweat were immediately replaced by water taken in the food, the remaining 1·4 kilogrammes gave rise to a permanent diminution in the excess of fluid in the body. It is, however, possible that the effect of the sweating was still greater, as it is not improbable that in cases of salt retention the percentage in the sweat rises. I am at present engaged in investigating this question.

When the object of producing diaphoresis is to prevent uræmia by causing the excretion of retained toxins by the skin, it is doubtful whether the hopes can be realised, as, although in such condition sweat contains an excess of nitrogenous substances, an excess in its toxicity has not yet been definitely proved. Moreover the immediate result of diaphoresis is an increased concentration of all the constituents of the blood, which may be the cause of the attacks of uræmia which occasionally follow excessive sweating.⁶⁹

Purgatives.—Purgatives which produce watery stools cannot as a rule appreciably affect œdema, as in most cases only traces of salt are excreted by the bowels. If, however, severe diarrhœa

⁶⁸ At a later period the same patient actually lost as much as 1450 grms. of sweat in a single electric light bath of one hour's duration.

⁶⁹ V. Leube in Penzoldt and Stintzing's *Handbuch der Therapie*, vii., 242. Third edition, 1903.

results, the effect on the œdema may become considerable, as in a case observed by Javal⁷⁰ in which 4 grms. of salt were excreted in one day in the stools. But the liability to intestinal complications in nephritis makes it unsafe to use purgatives in sufficient quantity to have such a marked effect. It is, however, doubtful whether it is wise to attempt to stop diarrhœa occurring spontaneously by means of drugs, as it may be looked upon as an attempt of the body to get rid of excessive salt and perhaps other substances, which the kidneys are unable to excrete in sufficient quantity.

Acupuncture.—If the power of the kidneys to excrete salt remains very small, a salt-poor diet can at the best result in the loss of very little retained salt, and sometimes actual retention may occur. In cases of this kind the lasting excellent effect of direct removal of some of the œdema fluid by acupuncture or by the use of Southey's tubes is partly explained by the loss of about 7 grms. of salt in each litre, for however bad the condition of the kidneys may be it would take a considerable time for 8 grms. to be once again retained if the strict diet was continued. Moreover well-marked œdema leads to compression of the venules and so causes a rise of pressure within them great enough to interfere seriously with the removal of the lymph, which probably takes place normally to a great extent by absorption into the venules. The flow of lymph in the lymphatics themselves will also be obstructed in a similar way. Finally the elasticity of the connective tissue, impaired by the stretching due to the œdema and perhaps partly by the same influences which diminish the permeability of the vessel walls, has an improved chance of returning to its normal condition, which is less favourable to the formation of œdema. These factors explain why the removal of part of the œdema fluid by direct means leads frequently to the rapid absorption of the remainder.

Saline Injections.—In uræmia rectal or subcutaneous injections of saline solution are often found to be useful, but where much œdema is present this will almost certainly be increased by

⁷⁰Semaine méd., p. 224, 1903. See also Kelly, Trans. of the Assoc. of Amer. Physicians, xx., 445, 1905.

the injection, and there is considerable risk of giving rise to pulmonary œdema. As the influence on the œdema is due to the salt contained in the fluid injected, all danger can be avoided without influencing the efficacy of the treatment by substituting an isotonic solution of dextrose for subcutaneous injection and plain water for rectal use.

SUMMARY.

1. Deficient power of the kidneys to excrete sodium chloride is an essential factor in the production of renal, cardiac and so-called "idiopathic" œdema.

2. The retention of salt acts by causing a secondary retention of water, which leads to a condition of hydræmic plethora.

3. Hydræmic plethora can only give rise to œdema if accompanied by increased permeability of the vessel walls.

4. Tissue changes, such as those described by Lazarus-Barlow and Bainbridge, probably are of no importance in the production of œdema. Diminished elasticity of the connective tissue may, however, aid in its formation, and in cardiac cases various mechanical factors are of importance.

5. Milk diet owes its reputation in the treatment of renal and cardiac œdema to its poverty in salt, and the value of diaphoresis depends mainly on the removal by the sweat of salt retained in the body.

6. A liberal mixed diet as poor in salt as possible results in as speedy a disappearance of œdema as a milk diet without producing any injurious effects. It has the additional advantages of preventing the impaired nutrition of the body caused by an exclusive milk diet and of putting the kidneys into as favourable a condition as possible for repairing the damage done to them.

MECKEL'S DIVERTICULUM AND ITS PATHOLOGY.

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MECKEL'S Diverticulum is of interest for several reasons, but chiefly so because it is not infrequently the cause of acute and often obscure abdominal lesions, in the diagnosis and treatment of which a knowledge of its anatomy and pathology is of the greatest importance.

As might be anticipated, in the clinical and post-mortem records of Guy's Hospital, examples of nearly all the anatomical peculiarities and of most of the morbid processes occurring in, or caused by, the diverticulum are to be found. I have compared the cases on which this paper is founded with the specimens in the various London museums, and with cases recorded in the various medical journals, to which reference is frequently made, though, of course, no attempt is made to give a complete bibliography.

Altogether, with cases recorded elsewhere and the cases from our own reports, I have made notes of about 360 diverticula, which for convenience in reference may be divided into two groups—(1) an anatomical group, where a diverticulum was present, but showed no pathological change; (2) a pathological group, where the diverticulum was the seat of, or the cause of, some pathological lesion.

Meckel's diverticulum is the persistent proximal portion of the vitelline duct, which at an early stage of foetal life forms a

communication between the primitive alimentary canal and the yolk sac. The part of the alimentary canal into which the duct opens is the mid gut, which is at first a short straight portion of the primitive intestine, the ventral aspect of which contains the wide opening of the vitelline duct. The mid gut grows enormously, and from it is developed a U-shaped piece of intestine suspended by a mesentery from the dorsal aspect of the abdominal cavity. From the proximal limb of the U is developed the jejunum and a portion of the ileum, while from the distal loop is developed the large intestine from the cæcum to the splenic flexure, with a variable portion of the ileum. The vitelline duct, now small and unimportant, opens into the intestine at the apex of the U, and the variable position of the diverticulum, when it persists, depends on the amount of the ileum formed from the distal part of the loop. The more of the ileum formed from this limb, the higher will be the point of origin of the diverticulum.

From the mesentery of the mid gut are developed the mesentery of the small intestine, the transverse mesocolon, and the ascending mesocolon, when that structure is present. Running in this mesentery is an artery—the vitelline artery—which, in the early stage of development, takes blood to the yolk sac, but later on, when this structure becomes functionless and atrophies, supplies the intestine from the commencement of the jejunum as far as the splenic flexure, and becomes the superior mesenteric artery.

Blood is brought back from the yolk sac by the two vitelline veins, the left of which disappears, while the right eventually becomes the superior mesenteric vein, the proximal part of both veins helping to form the portal vein. These vessels, in their course between the yolk sac and the mesentery, run along the lateral aspect of the vitelline duct.

The yolk sac in the human embryo soon loses its function and atrophies. This process starts peripherally and extends towards the ileum, so that normally there should be no trace of the duct in the fully developed fœtus. At the same time the vessels should also atrophy and completely disappear in that part of

their course beyond the mesentery. It is, however, of interest to find that in many mammals these vessels are still present at birth. Allen¹ found that in newly-born cats and dogs small vessels run across the peritoneal cavity from the umbilicus, one of which is connected with the superior mesenteric artery and the other with the portal vein. He suggests that this persistence of the foetal vessels may be due to the formation of adhesions between the yolk sac and the allantois, and that the two sets of vessels thus may communicate.

If the proximal end of the vitelline duct persists we have a Meckel's diverticulum. If traces of the obliterated foetal vessels persist, we have a fibrous cord which may or may not be pervious for part of its course. Either the duct alone may persist, or traces of the foetal vessels be found, or both may occur together, giving rise to a Meckel's diverticulum, from the distal end of which a fibrous cord is given off which is either attached to the umbilicus, or to the abdominal wall or some viscus, or may end freely in the peritoneal cavity. The lesions caused by the diverticulum and by the fibrous remains of the vitelline vessels must be considered together. Indeed, in many cases the trouble is due to the latter rather than to the former, especially in the causation of acute intestinal obstruction.

The presence of a diverticulum ilei has been recorded 81 times in our post-mortem records from 1885—1905 in 10,360 inspections. On 18 occasions it was either the cause of, or the site of some pathological change. Before 1885 its presence was rarely recorded unless it was associated with some pathological condition. As the presence of a healthy diverticulum is by no means always noted, these statistics do not give any true idea of the frequency of its occurrence. This question was investigated by a committee of the Anatomical Society in 1891, when a diverticulum was found to occur 16 times in 769 bodies examined, or 2.08 per cent. Mitchell, of Chicago,² found a diverticulum on 39 occasions in 1,635 successive post-mortems, or 2.38 per cent. Hence it may be taken that a Meckel's diverticulum is present in just over 2 per cent. of all human bodies.

A remarkable fact brought out by a study of these statistics is that the diverticulum persists far more frequently in the male sex than in the female. This is best shown by Mitchell's figures, since he records the number of male and female bodies examined. Thus in 1,330 male bodies he found a diverticulum on 35 occasions, or 2.63 per cent.; while in 305 female bodies it was present only 4 times, or 1.31 per cent. Of 175 cases of healthy diverticula of which I have notes, 121 were from male bodies, 29 from females, and in 25 the sex is not recorded. In the pathological series 120 were males, 34 females, while in 31 cases the sex is not mentioned.

It has been stated that the co-existence of other malformations may help in the diagnosis of Meckel's diverticulum as the cause of an abdominal lesion, but only once in all the above cases was any other deformity mentioned as being present, and that was a cleft in the soft palate.

In the adult the diverticulum usually opens into the ileum about three feet from the ileo cæcal valve, but its position varies very widely. Thus, it may be situated only an inch or two from the valve, or it may open high up in the jejunum according as very little or a great part of the small intestine is developed from the distal limb of the U-shaped loop of the foetal gut. It must, however, be distinguished from the diverticula which occur in the duodenum which have quite a different origin, being in all probability derived from abnormalities in the formation of the diverticula from which the liver and pancreas are developed. In an infant the average distance of the diverticulum from the ileo cæcal valve is about twelve inches. Its position in the abdominal cavity varies very much, since it is attached to a movable piece of intestine and projects freely among the intestinal coils, but generally speaking its position is on the right side and in the lower part of the abdomen. Dr. Coupland* records a case where a diverticulum four and a half inches long was directed upwards over the small intestine and great omentum, and rested in a groove on the anterior surface of the left lobe of the liver.

In length the diverticulum varies from five or six inches to a mere nipple-shaped projection from the ileum. Occasionally,

however, it may be much longer. A remarkable case is recorded by Bilton Pollard⁴ of a diverticulum, given off from the jejunum two feet beyond the pylorus. It was thirty-six inches long and ended blindly by becoming attached to the umbilicus. The small intestine terminated normally at the ileo cæcal valve, five and a half feet below the diverticular opening. In spite of its great length and high position, this diverticulum must be regarded as derived from the vitelline duct, which not only did not atrophy, but actually grew in length and diameter until it resembled a large piece of the small intestine.

The diverticulum usually opens at the free border of the ileum, but occasionally the aperture is lateral and the diverticulum may occasionally be adherent to the mesentery, or it may open laterally or close to the mesenteric attachment of the bowel. The opening is usually as large as the lumen of the ileum, so that intestinal contents can pass in and out quite freely. Occasionally, however—and this is usually associated with the lateral or mesenteric positions—a “spur” of mucous membrane is formed which may act as an imperfect valve. Also the diverticulum may be of greater diameter than continuation of the small intestine, which then has the appearance of coming from the side of the diverticulum. This again is more common when the opening has the lateral position.

These points are of great importance in considering the question of obstruction of the intestine from within at this position.

The diverticulum is usually conical or finger-shaped; not infrequently the end is dilated and bulbous, or hammer-shaped, and it may show several small secondary diverticula. Occasionally it may be spherical with a narrow neck and small aperture communicating with the intestine.

The diverticulum at times is provided with a short narrow mesentery which is derived from the true mesentery, its attachment crossing the ileum in order to reach the diverticulum. When this mesentery is present it frequently contains a large branch of the superior mesenteric artery, which doubtless has produced this fold of the peritoneum. A large artery may often be seen supplying the diverticulum, even when no mesentery is

present. This artery must be regarded as the remains of the primitive vitelline artery passing along the duct to the yolk sac.

Attached to the extremity or side of the diverticulum there is occasionally a fibrous cord, formed by the impervious vitelline vessels. The cord may be free in the abdominal cavity, but more frequently it is attached to the umbilicus, the abdominal wall, the mesentery, or to some viscus. The presence of this ligament, especially when it is adherent, greatly increases the likelihood of some pathological change taking place. Thus in the anatomical series it is attached only 9 times out of 145 cases, while in the pathological series the diverticulum was attached in 110 cases, while on only 51 occasions was it free in the abdominal cavity. In the cases recorded in the Guy's reports the place of attachment is as follows:—

To the mesentery	11
To the umbilicus (with fistula)	8
To the umbilicus (fibrous cord)	2
To a hernial sac	3
To the anterior abdominal wall	1
To the great omentum	1
To the broad ligament	1
To the right kidney	1

As this number of cases is not sufficient to give one a correct idea of the various attachments, the following are the positions of attachment of all cases of which I have made notes, including the Guy's cases quoted above.

To the umbilicus (with fistula)	32
To the umbilicus (by fibrous cord)	15
To the mesentery	32
To bowel	6
To the transverse meso-colon	1
To a hernial sac	5
To the bladder	1
"In the pelvis"	1
To the anterior abdominal wall	4
Near the internal abdominal ring	1
To the right kidney	1
To the broad ligament	1

A fibrous cord may pass from the extremity of the diverticulum and have its distal end attached, forming a typical arch, and yet give rise to no trouble. Thus Rolleston⁵ found a fibrous cord extending from the tip of the diverticulum with its other extremity attached to the ileum. Kelynak found similar bands passing from the diverticulum to the abdominal wall and pelvic peritoneum, and Mitchell, in his series of cases quoted above, found on two occasions a band passing from the extremity of the diverticulum to the root of the mesentery. In each case, however, the patient had escaped the danger of intestinal obstruction and had died from some cause unconnected with the presence of this dangerous arch.

A glance at the above statistics shows that, as might be expected, the commonest attachment of the diverticulum is to the anterior abdominal wall at the umbilicus either directly or by means of a fibrous cord. The other attachments may be brought about in various ways. Thus when it is adherent to a hernial sac this is due to chronic peritonitis with adhesion of the contiguous peritoneal surfaces. Probably in some other situations the adhesion is the result of chronic inflammation. Corner⁶ suggests that a chronic peritonitis around the diverticulum, or "chronic diverticulitis," is a frequent cause of the fixation of the diverticulum.

Sometimes the original attachment at the umbilicus may get torn through, the free end escaping into the peritoneal cavity, and subsequently becoming adherent elsewhere. A very common arrangement, however, is for a fibrous cord to leave the distal extremity or the side of the diverticulum, and after a short course through the peritoneal cavity to become attached to the root of the mesentery between the base of the diverticulum and the cæcum. The frequency of this arrangement suggests a definite cause, and has been thus explained by J. E. Thompson.⁷ It has been pointed out above that the diverticulum not infrequently is provided with a mesentery, connected with the mesentery of the ileum, and raised up by the vitelline vessels in their course from the mesentery to the vitelline duct. If these vessels become transformed into a fibrous cord, and the mesentery between them

and the diverticulum, which is always very thin, becomes absorbed, we should then get a fibrous cord passing from the extremity of the diverticulum to the root of the mesentery. Two facts may be quoted in support of this view:—(1) A pervious branch of the superior mesenteric artery sometimes runs in the fibrous cord; (2) The position of the mesenteric attachment of the cord closely corresponds to the termination of the superior mesenteric artery. Thus the space beneath the fibrous arch through which a coil of intestine is so likely to slip is usually an aperture due to absorption of the diverticular mesentery and not a space beneath a band of inflammatory adhesions.

* Occasionally Meckel's diverticulum may completely atrophy and yet some trace of the vessels remains as a fibrous band. One of the common positions for the "solitary band" which occasionally causes acute intestinal obstruction is at the root of the mesentery near the cæcum, and though this is sometimes the result of a local peritonitis or of an old caseous mesenteric gland, yet, as Sir Frederick Treves suggests (*Intestinal Obstruction*, p. 17), many cases are instances of a diverticular ligament. Leichtenstern describes the existence of a congenital ligament in the form of a solid fibrous band passing from the intestine to the root of the mesentery as of frequent occurrence.

The mesentery of the lower ileum is a common situation for apertures in the mesentery through which the intestine may be strangulated. The margin of the slit is sometimes smooth with no sign of peritonitis or history of injury, thus suggesting a congenital origin. Treves mentions such an aperture (*Intestinal Obstruction*, p. 52), the margin of which was a dense band containing a branch of the superior mesentery artery. Possibly some of these apertures may be due to absorption of the mesentery to one side of the diverticular ligament: such an aperture would be comparable with the space beneath the fibrous arch described above.

In structure Meckel's diverticulum resembles the intestine from which it springs, though its walls are usually thinner. The mucous membrane shows villi, and small valvulæ conniventes; lymphoid follicles and even Peyer's patches may also be present.

When a healthy diverticulum is found at a post-mortem it usually contains gas, but may also contain *fæcal* matter.

The pathological changes which may occur in the diverticulum, or which may result from its presence or the persistence of its vessels in the form of fibrous cords, may be classified in the following way. The various lesions will be considered in this order.

1. At the umbilicus :—
 - a* Fæcal fistula.
 - b* Fæcal fistula in adults.
 - c* Tumours composed of granulation tissue and everted mucous membrane.
 - d* Umbilical polypus.
 - e* Carcinoma of the umbilicus.
 - f* Intussusception protruding from the patent diverticulum.
 - g* Umbilical cysts.
2. Inflammation of the diverticulum :—
 1. Chronic inflammation.
 2. Acute inflammation.
 - a* Associated with a concretion or foreign body.
 - b* Due to torsion of the diverticulum.
 - c* Compression, occurring alone or with simultaneous compression of the small intestine.
 - d* Cause doubtful.
3. Tumours of the diverticulum :—
 - a* Polypus.
 - b* Lipoma.
4. Ulceration of the diverticulum :—
 - a* Typhoid.
 - b* Tuberculous.
 - c* Sloughing and perforation.
5. Causing intestinal obstruction.
 - a* Congenital atresia
 - b* In a hernial sac (Littre's hernia).
 - c* Obstruction from within by a foreign body
 - d* Obstruction by a band formed by the diverticulum and its ligament.
 - e* Strangulation by knotting.
 - f* By traction on, or by causing a volvulus of the coil to which it is attached.
 - g* By pressure of the distended diverticulum.

6. Invagination of the diverticulum :—
 - a* Forming a polypoid tumour.
 - b* Causing chronic intussusception.
 - c* Causing acute intussusception.
7. Injury of the diverticulum.
 - a* Rupture.
8. Possible results of persistence of traces of the diverticulum or its ligament :—
 - a* The solitary band.
 - b* Formation of a mesenteric cyst.
 - c* Causing an aperture in the mesentery.
 - d* Causing duplication of the intestine.

Fæcal fistula.—There can be no doubt that of all the troubles resulting from the presence of the persistent diverticulum, an umbilical fæcal fistula, often associated with a small polypoid tumour, is the commonest. It is difficult, however, to decide as to the relative frequency of a fæcal fistula, compared with the rarer lesions associated with the persistent diverticulum. The fistula may close spontaneously, or after the application of the cautery, and the polypoid tumour when snipped away may give rise to no further trouble. Hence the greater number of these cases are treated in the out-patient department and are not recorded in the permanent reports of the hospital. The fistula may, however, be very large, or it may reappear after treatment with the cautery, or it may be associated with extensive prolapse of the mucous membrane, in which cases further treatment will be required. The mechanism of the production of this fistula is well known. The diverticulum may be adherent to the amniotic covering of the umbilical cord, or it may project into the cord beyond the abdominal wall. The diverticulum then becomes included in the ligature, and hence the fistula commonly appears when the stump of the cord separates. It may, however, appear some days later, when it commonly follows on some septic process at the umbilicus.

When the fistula is large two important changes may occur in the intestine.

1. The opening may be so large that the whole of the fæcal matter is discharged through the fistulous opening, none passing

on to the intestine below. When this happens the whole of the large intestine and the part of the ileum below the diverticulum, owing to the loss of function, become very small and contracted. This point must be remembered in the treatment of such a case, for a plastic operation for the closure of the fistula is not likely to be successful when the intestine below is too small to transmit the intestinal contents.

2. The mucous membrane may prolapse through the opening, forming a polypoid tumour composed of hypertrophied mucous membrane and granulation tissue, with an aperture discharging fæces on its surface. When the diverticulum is short and wide it may become completely everted, the result being a red hemispherical tumour which may show *valvulæ conniventes* and having on its surface two openings—a large one, discharging fæces, and a small one, which it may be difficult to find, and from which no fæces escape, leading downwards to the large intestine. Obviously in this condition no fæcal matter can pass to the intestine below, which will thus most certainly be narrow and badly developed. Occasionally, as an intermediate condition, there may be a spur-like process of the mucous membrane of the ileum, which only allows a small portion of the fæces to pass along the normal channel.

Bridgdon⁹ reports the case of an infant which defæcated normally for ten days, after which fæcal matter began to pass from the umbilicus. Later on the whole of the fæces passed here, and the diverticulum becoming completely everted, two openings were seen on the projecting mass, from the larger of which the fæcal matter came. The eversion of the diverticulum was reduced, but owing to the small size of the intestine below, no attempt was made to close the artificial anus, though its edges were drawn together by strapping, thus causing some of the fæces to pass along the normal channel. At a second operation the diverticulum was excised and the child recovered.

A similar case is reported by Guthrie,¹⁰ who found that the intestine below the diverticulum had only the diameter of a lead pencil.

When there is a complete eversion of the patent diverticulum showing these two openings for the proximal and distal portions of the gut, a further complication may occasionally ensue. The ileum above and below may become completely prolapsed at each of the two openings on the mucous surface of the everted diverticulum, thus giving rise to two finger-like projections with an aperture at their extremities communicating with the lumen of the intestine. This condition must be carefully distinguished from the tumour of very similar appearance caused by the passage of an intussusception through the patent diverticulum, which is described below. This condition is comparable with complete prolapse of all the coats of the rectum at the anus. E. A. Moreshed¹⁶ reports two cases in which this had occurred. In one of his cases the prolapsed portions of ileum gave rise to two sausage-shaped tumours measuring two and four inches in length, while in the other both tumours were four inches long and the gut was almost gangrenous. Both these cases died, though in the second case the tumours were reduced and the gangrenous portion of the gut was excised.

Cases 3, 4, and 6,* are examples of umbilical fistula treated by excision of the diverticulum.

When the diverticulum is excised it should be ligatured close to its intestinal attachment, and the stump should then be invaginated into the lumen of the gut by means of Lambert's sutures.

When removing an umbilical polypus by scissors, especially when associated with a faecal fistula, the possibility of opening the general peritoneal cavity must always be borne in mind. When the diverticulum is everted it is very common for a ring-shaped cul de sac of the peritoneum surrounding its base to protrude beyond the umbilical ring. Injury of this process has occasionally resulted in death from peritonitis. Case 1 described by King¹¹ is of interest, for here, though the fistula was successfully closed by a plastic operation by Aston Key, the patient subsequently died with intestinal obstruction. The specimen which is in the museum shows a diverticulum passing from the closed

*These numbers refer to the cases abstracted on page 314.

umbilicus to the ileum, while the obstruction is due to an intestinal coil having passed under a fibrous band close to its base and probably a relic of the proximal part of the vitelline vessels. King also mentions a case (2) where death was caused by the umbilicus giving way in a bronchitic child and coils of intestine escaping through the aperture.

It may here be pointed out that when a true congenital umbilical hernia is present, a Meckel's diverticulum, if present, will form one of the contents of the sac, which always consist of the portions of intestine developed from the lowest part of the primitive U-shaped loop. The diverticulum has been found adherent to the sac of a congenital umbilical hernia; this is of interest, as it throws light on the causation of a fæcal fistula, since adhesions between the diverticulum and the coverings of the umbilical cord must have occurred during foetal life.

Several cases have been recorded of adults, previously quite healthy, with no history of peritonitis or of any previous trouble at the umbilicus, developing a fistula, preceded by signs of suppuration and discharging a little fæcal matter, or possibly even a fæcal concretion with some pus. The fistula closes after the discharge has taken place, and the patient remains in good health subsequently. Possibly this may be due to suppuration occurring in the distal part of a Meckel's diverticulum, the proximal part of which is either completely closed or opens into the gut by only a small aperture. Case 7 may possibly be explained in this way, though it has not been possible to trace the after history of this patient. Similar cases have been described by G. Heaton¹² and G. R. Tambe,¹³ in both of which cases fæcal concretions were discharged through a fistulous opening which subsequently closed.

Umbilical tumours.—Tumours composed of prolapsed mucous membrane and granulation tissue, associated with the presence of a fæcal fistula, have been described above. Occasionally polypoid tumours are present without any fistulous opening. These tumours, which may be pedunculated or sessile are usually of a bright red colour. Histologically these tumours are composed of fibrous tissue with some unstriated muscular fibres, and

contain Liebukuhn's follicles lined by the typical columnar cells. Case 5 is a very good example of this condition.

The umbilicus is occasionally the seat of a malignant growth. When primary this is usually an epithelioma, while occasionally it is the seat of secondary growths, the primary growth being in some abdominal viscus. Several cases of columnar-celled carcinoma, apparently primary in nature, have been recorded in this situation. These have been explained by assuming that the growth has occurred in some vestige of the vitelline duct. This is supported by the well-known fact that malignant growths may occur in other foetal relics, such as the branchial clefts and thyro-glossal duct, though the occurrence of any malignant growth in the remains of the vitelline duct is certainly extremely rare.

C. D. Green¹⁴ describes a warty growth the size of a marble removed from the umbilicus of a woman æt. 60. Histologically the tumour was covered by stratified epithelium and composed of a stroma of fibrous tissue and unstriated muscle fibres, contained in which were glandular elements, some resembling Liebukuhn's follicles and others distended with gelatinous material. The majority of a committee of the Pathological Society decided that the growth was malignant, and that if primary it was probably derived from some remnant of the vitelline duct. The patient recovered, and the question of the primary nature of the growth remained undetermined.

A similar case, with the same unsolved question as to the primary nature of the growth, is reported by Maylard.¹⁵

Occasionally an intussusception may project through an umbilical fistula in the same way that it may present at the anus. This can be distinguished from the condition above described as prolapse of the mucous membrane diversion of the diverticulum, in the same way that a prolapse may be distinguished from an intussusception at the anus. A probe can be passed into the lumen of the bowel at the side of the projecting mass as well as through the aperture at the apex of the intussusception. When the diverticulum is everted a probe can be passed along the one or two openings, according to the extent of the eversion, but not along the outer margin of the projecting mass. A

remarkable case (8), showing this rare condition, was admitted into Guy's in 1895, under Mr. Golding-Bird. In this patient the intussusception was retrograde and fæces escaped between the presenting tumour and the wall of the diverticulum.

Very rarely the proximal part of the vitelline duct may atrophy, but its distal extremity may persist and afterwards becoming dilated give rise to a cyst. This may project at the umbilicus, when it may be mistaken for the sac of an umbilical hernia, or it may be contained within the abdominal cavity, though adherent to the abdominal wall at the umbilicus. In either case a fistulous opening is likely to result, either spontaneously or after surgical interference. This fistula, however, differs from the fistula described above in that, as the opening into the ileum is obliterated, the discharge will not be fæcal, but rather resembles the succus entericus. Usually clear yellow fluid escapes, and as the cyst may attain considerable size there may be a history of fluid gushing away when the child cries or uses its abdominal muscles. The escaping fluid is easily mistaken for urine, and the condition will then be erroneously regarded as a patulous urachus. It may, however, be distinguished from urine by its alkaline reaction, its soapy feel, and also that it contains no urea and is albuminous. In one of Moreshead's cases quoted above, it is stated that although the diverticulum was patent for its whole length, thus communicating with the ileum, yet yellow fluid escaped which was thought to be urine as it had no fæcal odour. Later on, however, two sausage-shaped protrusions appeared through the fistulous opening, thus rendering its nature obvious. The correct treatment of these cases is to dissect away the whole of the cyst. Histologically the cyst wall has the structure of small intestine. I have not been able to find a typical case of this condition in the Guy's reports.

Heaton,¹⁷ however, describes the case of a boy æt. 4½, who had an umbilical fistula which followed the removal of a polypus. A probe passed downwards and backwards for three and a-half inches, and from the opening yellow alkaline soapy fluid escaped. The cyst was removed and was found to have a solid fibrous band

passing from its deep aspect to the small intestine. Microscopically the wall of the sac had the structure of small intestine.

Inflammation of Meckel's Diverticulum.—This subject has been discussed by Corner^e in the Erasmus Wilson Lectures for 1904 on Acute Infective Gangrenous Processes in the Intestine. The inflammation may be acute or chronic. Chronic inflammation, or "chronic diverticulitis," results in the formation of adhesions between the diverticulum and the surrounding viscera. Corner regards this as a frequent occurrence, but it has been shown above that in many cases the attachment of the diverticulum may be otherwise explained. Chronic inflammation leading to the formation of adhesions between its peritoneal coat and the adjacent peritoneum frequently occurs when it is contained within a hernial sac.

A number of cases of acute inflammation of the diverticulum have been recorded, and to understand these cases it is necessary to compare it with the appendix. Both these structures are blind projections from the alimentary canal, but whereas acute inflammation of the latter is very common, it is rare with the former. The reason of this is doubtless, as Corner points out, that the diverticulum opens into the ileum quite freely, the diameter of the opening being usually equal to that of the adjacent ileum. Intestinal contents can thus pass quite freely in and out. In the situation of Meckel's diverticulum, too, there is not that natural stasis of the intestinal contents which exists in the cæcum. It has, however, been pointed out that occasionally there may be some chronic obstruction to the flow of faecal matter in the former situation which may be due to a valvular fold of mucous membrane, or to an actual narrowing of the intestinal canal either at, or just below, the opening of the diverticulum. Again, since the diverticulum projects freely into the abdominal cavity it may become twisted or compressed, and following on the obstruction to its blood supply acute inflammation with gangrene and perforation is likely to follow. It may be here pointed out that as the diverticulum is usually situated low down on the right side of the abdomen, acute inflammation is likely, clinically, to closely resemble acute appendicitis, which

diagnosis has been made in a large proportion of the recorded cases, the true nature of which has only been ascertained at an operation or in the post-mortem room. I have notes altogether of twelve cases of acute inflammation of the diverticulum: of these ten were in males, in one the sex was not mentioned, and the other was in a female patient. The ages of ten of these patients varied between four and fourteen years, the other two being twenty-four and twenty-seven years of age.

Four cases (Nos. 9, 10, 11, and 12) are recorded in our clinical and post-mortem records. All of these occurred in males, and the ages of the patients varied between five and twenty years.

The following varieties of acute inflammation of the diverticulum may be distinguished:—

1. Associated with the presence of a concretion or of a foreign body.
2. Due to twisting of the diverticulum.
3. Due to compression of the diverticulum, usually associated with strangulation of the small intestine beneath it.
4. Cause doubtful.

Any of these are likely to be followed by perforation or sloughing of the diverticulum and general peritonitis, though rarely a localised peritoneal abscess may result. A distinction must be made between a foreign body causing ulceration and perforation and a foreign body causing intestinal obstruction at the narrow spot which may be present in the ileum just below the opening of the diverticulum. Several cases of the former condition have been recorded, though none are to be found in our post-mortem reports. Doran¹⁹ describes a case of a male child, *æt.* 4, who had acute abdominal pain associated with vomiting and constipation after eating peas. The boy died, and at the post-mortem general peritonitis was found caused by a perforation in a Meckel's diverticulum which contained a pea. Beale²⁰ records a case where a bulbous diverticulum hanging into the pelvis showed a perforation three-eighths of an inch in diameter, through which a cherry stone, some orange pips, and two faecal concretions had passed, causing a fatal peritonitis. Magaigne and Blanc describe a case where the diverticulum contained a fish bone.

In Case 27, a faecal concretion the size of a cherry and containing "fruit skins" was found in the diverticulum, though here the trouble was due to a coil of intestine having slipped beneath a fibrous band attached to the diverticulum.

The diverticulum may be twisted on itself and become gangrenous. Taylor (Bull, John Hopkins Hospital, 1901) records such a condition in a girl *æt.* 6. At an exploratory laparotomy a diverticulum was found twisted on itself three times, forming a tumour the size of a potato, which was attached to the ileum by a narrow pedicle.

A localised peritoneal abscess may result without any definite perforation of the diverticulum. Boldt²¹ records such a case in a female patient who, in addition to pain in the right iliac fossa, suffered from profuse leucorrhœa. When the abdomen was opened numerous adhesions were found in the pelvis. While these were being separated a collection of pus was found "resembling an appendicular abscess." Projecting into this was a structure which at first was thought to be an appendix, but on tracing it to its attachment it was found to proceed from the small intestine, and on further examination the appendix was found to be normal. The diverticulum, which was regarded as the cause of the abscess, was excised and the patient recovered.

Frequently no definite cause for the inflammation is found, and the case then usually resembles clinically one of acute appendicitis, and this is the diagnosis usually made. The four cases of acute inflammation of the diverticulum recorded in our post-mortem reports are all of considerable interest. In case 12, there were numerous adhesions around the inflamed diverticulum. A coil of small intestine had become entangled in these, but is said not to have been strangulated. In case 11, no definite diagnosis is recorded in the clinical report, though from the account of the symptoms and the condition of the patient there was certainly a close resemblance to appendicitis. Mr. Dunn operated and found numerous adhesions around the diverticulum, and below it the intestine was collapsed. There were also some adhesions around the appendix, but these appear to have been all of long standing. Some doubt was expressed as to whether

the peritonitis was the result of diverticulitis or of appendicitis, but on carefully reading the clinical and post-mortem reports the former seems the more probable.

Gangrene and even entire separation of the diverticulum not infrequently occurs when a coil of intestine becomes strangulated under the arch formed by the diverticulum when this is attached to the mesentery by its ligament. When this happens the blood supply of the diverticulum is interfered with as well as that of the strangulated coil and it frequently suffers to an even greater extent than the ensnared gut. The diverticulum is then likely to become gangrenous, while the compressed intestine may still be in a recoverable condition. Corner, in the lecture quoted above, suggests that in many cases this may be the true explanation of a gangrenous diverticulum, when no obvious cause is found at the operation or post-mortem. If the diverticulum sloughs before the intestine is damaged, the coil of bowel will be released and may regain its normal appearance. In such a case on opening the abdomen there will be found a gangrenous diverticulum giving rise to peritonitis. Case 9, under Dr. Fawcett and Mr. Steward, certainly shows that this sequence of events may occur. The clinical history is one of acute intestinal obstruction. At the operation the peritoneum contained turbid yellow fluid, and a coil of intestine was found strangulated beneath a diverticulum adherent to the great omentum. The intestine itself was in a recoverable condition, but the diverticulum, which was sausage-shaped, showed gangrenous areas alternating with patches of lymph. The diverticulum which was removed is now in the Gordon Museum.

Had the operation been performed later one can quite understand that the diverticulum might have completely separated, and the case would probably have been regarded as a primary acute inflammation of this process.

It is thus seen that it is impossible to absolutely separate these cases from those to be described later, where the small intestine is ensnared beneath a band derived from the diverticulum and its ligament. In cases 20, 21, and 24, which clinically were

cases of acute intestinal obstruction, the diverticulum showed gangrenous areas. This fact, which was first pointed out by Dr. Hilton Fagge,³⁹ may also explain why in so many recorded cases of strangulation beneath this band with acute symptoms it is noted at the post-mortem that the strangulated intestine was not seriously damaged, and that it was quite easily drawn from beneath the fibrous arch.

In case 10 there is a history of old appendicitis, and the sloughing of the diverticulum was attributed to it having become ensnared beneath a band of old adhesions.

Tumours.—Meckel's diverticulum having the same structure as the small intestine we should expect to find it equally liable to the presence of growths. These, however, are extremely rare. I remember the late Dr. Bryant finding at a post-mortem a diverticulum containing a polypus, but cannot find the post-mortem report.

Dr. Zum Busch has recorded a case where a small lipoma was found in a Meckel's diverticulum which had become invaginated and caused an intussusception. It will also be shown later on that the diverticulum itself may give rise to a polypoid tumour.

It might be thought that as the diverticulum is the remains of a foetal structure, it might occasionally be the seat of malignant growths; no such case is, however, to be found in our reports, and beyond the two cases of umbilical carcinoma quoted above, I know of no museum specimen or definite recorded case.

Ulceration.—Tuberculous ulceration may occur, associated usually with phthisis and with tuberculous ulceration of the small intestine, and of characteristic appearance. Cases 13 and 14 are examples of this condition, which, however, gave rise to no special symptoms. There is a specimen in the London Hospital Museum showing extensive tuberculous ulceration of the ileum and cæcum, with a perforating tuberculous ulcer of a Meckel's diverticulum. Three perforations were also present in the ileum.

The diverticulum occasionally shows a well-marked Peyer's patch, and so may show typhoid ulceration. Galton²² records

a case where typhoid ulceration in the diverticulum had led to a fatal perforation.

Ulceration and perforation also occur in the acute inflammatory conditions already described.

Mr. Makins²³ describes a diverticulum which post-mortem showed thirteen perforations, some of the openings being sharply cut, while others were bevelled at the expense of the mucous coat. It was not certain whether the perforations resulted from a process starting in the diverticulum itself, or whether they were due to local gangrene, the result of pressure.

Meckel's diverticulum as a cause of intestinal obstruction.—This is one of the most frequent troubles resulting from the persistence of the diverticulum. It may be brought about in a number of different ways, and the obstruction may be caused shortly after birth or not until adult age is reached.

Congenital intestinal atresia.—The commonest place for congenital occlusion of the small intestine is a short distance above the ileo-cæcal valve in a position corresponding to the junction of the vitelline duct with the small intestine. Several different varieties of occlusion in this situation are known. The small intestine may end blindly near the lower end of the mesentery, and the large intestine start blindly usually on the right side just below the liver, there being no connection between the two blind extremities of the gut. There is no specimen of this condition in the Gordon Museum, though a number of examples have been recorded.

Jackson Clarke²⁴ records the remarkable case of a male child with a double hydrocele which was reducible on the left side, but only incompletely so on the right. Symptoms of obstruction were present, and an incision was made over the irreducible mass in the right groin. When the peritoneum was opened a number of white vermicelli-like bodies escaped. At the post-mortem examination the small intestine was greatly distended, and the coils were matted together by lymph, and large numbers of the vermicelli-like bodies were present in the peritoneal cavity. The small intestine ended blindly close to the cæcum, and at its extremity was a ragged opening through which spiral coils of

meconium passed into the peritoneal cavity, thus giving rise to the vermicelli-like structures which were composed of bleached meconium. The perforation was attributed to an injury received during parturition.

In other cases the small intestine may end blindly and from its extremity an impervious fibrous cord pass to the commencement of the large intestine. Case 33, which is preserved in the Gordon Museum, is an example of this condition.

Occasionally a membranous partition is found in the gut in this situation. In case 34 such a partition occurred nine inches above the ileo-cæcal valve. This specimen is also in the museum.

In all these cases the small intestine is very dilated, and the large intestine below the occlusion, while usually normal in structure, is thin-walled and small, and contains only a little whitish mucus. The poor development of the large intestine does not allow of any lateral anastomosis, and the treatment, uniformly unsuccessful, is to make an artificial anus at the lowest part of the distended small gut.

There can be no doubt that these congenital malformations are associated with the presence of the vitelline duct. They may be explained as an excess of the normal process of atrophy of the duct extending to the adjacent part of the intestinal canal. It is interesting to note that congenital occlusions of the duodenum also occasionally occur, and that, as has been pointed out above, diverticula are occasionally found also in this situation.

Meckel's diverticulum strangulated in a hernial sac.—This variety of hernia is known as Littré's hernia, and must be distinguished from Richter's hernia, where a portion of the circumference of the intestine is strangulated, but the whole lumen of the bowel is not obstructed. In addition to a Littré's hernia, the diverticulum is also found occasionally as one of the contents of the sac of a congenital umbilical hernia. I have notes altogether of eleven cases of Littré's hernia, and find that six of these were males and five females. The ages of the patients varied between three and seventy-seven years. The hernia may be inguinal or femoral, and situated on either the right or left side. The diverticulum may be the sole structure

contained within the sac, or there may, in addition, be small intestine or omentum. Clinically these cases present the same features as an ordinary strangulated hernia, though in some reported cases it is mentioned that the bowels acted naturally, as is not infrequently the case with Richter's hernia. In other cases, however, constipation is complete, and it is noted that the bowel below is contracted, while that above is abnormally distended. Of the cases of Littré's hernia treated at Guy's, case 31, which was under Sir Henry Howse, shows an interesting condition, for not only was the diverticulum contained within the hernial sac, but from it a cord passed to the root of the mesentery. Through the loop thus formed a portion of the ileum between the origin of the diverticulum and the ileo-cæcal valve had passed, but at the autopsy this coil was found not to have been strangulated.

The diverticulum may be adherent to the hernial sac, as in cases 29 and 32. J. E. Thompson reports (*Annals of Surgery*, Vol. xxvii.) the case of a male patient who attempted to reduce a hernia of some years' standing. The following day his condition necessitated an operation. The sac was then found to contain foetid gas, intestinal contents and pus. A search for a perforation was unsuccessful, and death resulted from general peritonitis. At the autopsy a rent was found at the base of a Meckel's diverticulum, the apex and sides of which showed old adhesions. There can be no doubt that here the patient, in reducing a Littré's hernia, in which the diverticulum was adherent to the sac, injured the diverticulum and so set up the fatal peritonitis.

Dowse²⁵ records a case where an artificial anus spontaneously formed in a female patient with a Littré's hernia. The hernia was irreducible, and though she vomited, yet there was not complete constipation. Two weeks later a brawny swelling appeared in the groin, which eventually burst, and allowed faecal matter to escape. She died three months later, when a diverticulum was found adherent to the sac of a direct inguinal hernia. A fistulous opening existed between the diverticulum and the skin. No foreign body was found, but doubtless the ulceration of the diverticulum was brought about by retained intestinal contents.

Meckel's diverticulum may be present in a hernial sac, without any signs of strangulation. Case 32 is an example of this condition. This patient was admitted for cirrhosis of the liver, and the hernia gave rise to no symptoms.

Obstruction from within by a foreign body.—In discussing the anatomy of the diverticulum it has been pointed out that the ileum is often narrowed at this spot. Hence we might expect that obstruction from a foreign body becoming impacted at this spot might occur. This, however, is very rare, and no case could be found in our post-mortem or clinical reports. Such a case, combined with compression of the intestine by the diverticulum, has been recorded by R. J. Pye-Smith in a boy æt. 13, on whom he operated for acute intestinal obstruction. A diverticulum was given off from the ileum in the usual position midway between the mesenteric and free borders of the intestine, a position especially likely to be associated with a narrowing of the lumen of the bowel. This passed through an opening in the mesentery and then encircled the bowel close above its own point of origin, its extremity being attached to the mesentery just above the opening. The constriction was divided and the collapsed bowel below immediately began to fill. In the first motion passed after the operation was a fish spine, triangular in shape with a sharp projection at each angle. The obstruction was attributed to this foreign body having caught at the obstructed spot. The boy had eaten fish a short time before symptoms appeared.

In the museum of the London Hospital there is a preparation showing a plum-stone impacted just at the point of origin of the diverticulum. A fatal obstruction was brought about partly by this and partly by kinking of the ileum at this spot by the diverticulum which was attached to the umbilicus.

Strangulation of intestine under the diverticulum.—This is the commonest way in which the diverticulum can cause intestinal obstruction, and there is no doubt that if the diverticulum is fixed at its distal as well as its proximal extremity, that it is a far more dangerous structure than when it hangs freely in the abdominal cavity. Occasionally an attached diverticulum is accidentally found at a post-mortem examination without having

caused any trouble, and I have found several cases recorded where not only is the diverticulum attached, but a coil of intestine has been found beneath it, but not strangulated. Case 16, where the patient died of peritonitis and pelvic cellulitis, secondary to perforation of the bladder from calculous cystitis, is an example of this condition. Case 30, where the diverticulum was contained in a hernial sac, shows a similar snaring of intestine beneath the band without strangulation.

I have collected notes of 45 cases of strangulation under the diverticulum. Of these, in 22 cases it was attached to the root of the mesentery, in 19 to the umbilicus, in 3 to small intestine, and 1 each to the transverse meso-colon, the broad ligament, the right kidney and the anterior abdominal wall.

An unusual mode of the formation of the obstructing band is recorded by Greenhow.²⁶ A short fibrous band extended from the umbilicus to the extremity of a diverticulum. This was provided with a mesentery, in which ran a fibrous band from the apex of the diverticulum to the root of the mesentery of the ileum. An opening existed in the mesentery of the diverticulum between it and the fibrous band. Through this opening a coil of ileum passed, which was collapsed, though apparently not strangulated. This is of very great interest from the light it throws on the nature of the fibrous band, and also that the coil passes through an aperture in the mesentery of the diverticulum. It has been already pointed out that in most cases this is the true nature of the loop formed by the diverticulum and its ligament. The portion of the intestine strangulated when the ligament is attached to the mesentery is almost invariably a part of the ileum below the diverticulum between it and the ileo-cæcal valve. In case 25, however, the strangulated portion was the ileum immediately above the origin of the diverticulum. When the diverticulum is attached to the umbilicus or elsewhere, the strangulated portion of gut is small intestine, though the position of this is rarely definitely stated. Not infrequently the strangulated coil is twisted on itself, and occasionally the diverticulum is twisted on its own axis.

This variety of intestinal obstruction is much more frequent in males than females. In 45 cases of which I have collected notes, 36 are males and only 9 females. The age varies considerably, but generally speaking it may be said to usually occur in young adults, but is by no means uncommon in children.

Clinically the obstruction is nearly always acute, though occasionally it may be subacute, and in a few cases there is a history of previous attacks of vomiting and constipation which have been successfully treated by drugs. A previous history of attacks of colic is found in case 23. The more chronic cases are likely to occur when the diverticulum is attached to the umbilicus.

As the result of the constriction the coil beneath the band may become gangrenous, but, as has been pointed out in discussing inflammation of the diverticulum, this also is likely to have its blood supply interfered with to an even greater extent, and so to become gangrenous and even to completely separate from the small intestine. Cases 9, 20, 21, 24 all show this condition.

To definitely diagnose the cause of the obstruction is usually impossible. As has been pointed out, the co-existence of other deformities is so rare that it is of no assistance. Occasionally, however, a history of an umbilical fistula in infancy may be obtained. This was known to have occurred in case 1, and a case is recorded by Sydney Jones²⁷ where the presence of the diverticulum causing acute obstruction was diagnosed in a man æt. 26, from the fact that there had been a fæcal discharge in infancy from the umbilicus.

The ligament in its passage from the diverticulum may, where it crosses the ileum to reach the mesentery, cause some constriction of the bowel, though not to such an extent as to cause acute obstruction. A good example of this condition is seen in case 22. The preparation in the museum (1072) shows a fibrous cord four and a half inches long, passing from the diverticulum to the mesentery, and distinctly grooving the ileum as it crosses it. No symptoms of acute obstruction were present.

The diverticulum and its ligament usually form only a short band, but occasionally it may be long and lax. When this is

so it may be thrown into a loop through which a coil of ileum slips, and is subsequently tightly gripped by the loop. Case 25 is an example of this condition.

Though it is easy to understand how the obstruction is brought about when the diverticulum is attached to the mesentery, it is not so easy to understand how the obstruction is produced when the attachment is to the umbilicus, for instead of the small fibrous arch found in the former condition, there is here a considerable space beneath the band. There are certainly several ways in which this may happen. In case 24 the coil of ileum between the diverticulum and the ileo-cæcal valve had passed over the band and was "coiled and hanging down in the pelvis." A very similar condition was recorded by Mr. Ward.²⁸ Here two loops of the lower part of the ileum had fallen over a diverticulum attached to the linea alba, and the mesentery in connection with these had been twisted on its axis. In these cases the bowel was probably kinked by the diverticulum. A similar case is described by Gibson Hamilton,²⁹ where two and a half feet of the ileum between the ileo-cæcal valve and the diverticulum had become twisted twice round that process as it passed between the ileum and the umbilicus. In other cases the diverticulum appears to cause a gradual kinking of the ileum at its attachment. This would explain the rather chronic nature of the symptoms in some of these cases. Possibly the obstruction in case 23 was brought about in this manner.

Strangulation by the diverticulum and its ligament becoming knotted round a coil of intestine.—No specimen of this rare condition is present in the Gordon Museum, and I have not been able to find any case in the clinical or post-mortem reports. The mode of formation of the knot is described by Sir Frederick Treves (Intest. Obst., p. 40). He points out that for the production of these knots it is necessary that the diverticulum shall be long, and that its distal extremity shall be free and provided with an ampulla. The presence of this ampulla is of great importance in making the knot sufficiently tight to cause obstruction in the surrounded coil.

This knotting of the free diverticulum must be distinguished from those cases described above where a coil of intestine passes through and is strangulated by a loop formed by a diverticulum with a long and lax ligament which is attached at its distal extremity.

Volvulus of the coil of intestine to which the diverticulum is attached.—In this variety of obstruction the diverticulum is long, and its distal extremity must be attached. The attachment may be to the umbilicus, but in a case recorded by Gill⁴⁵ the distal attachment was to the bladder. The volvulus in this occurred in the ileum just at the place where the diverticulum joined it.

The diverticulum may itself become twisted and so occlude the ileum at its point of origin.—In this condition the distal part of the diverticulum is distended and cyst-like, while its proximal part where it opens into the ileum is narrow. A remarkable case in which this condition had occurred in utero is described by T. Carwardine.³⁰ A large cystic diverticulum had become twisted on its own axis three times just where its narrow stalk joined the ileum. As the result of this, the ileum below the diverticulum had become transformed to an impervious fibrous cord. Above, the small intestine was enormously dilated, while the last twelve inches of the ileum, the cæcum, and colon were small and empty. A bristle could be passed from the dilated upper part of the ileum, along the twisted neck into the cystic extremity of the diverticulum, which was distended with meconium. The case recorded by Taylor,³¹ and mentioned above under inflammation of the diverticulum, is somewhat similar. Here the neck of a cystic diverticulum, resembling a potato in shape and size, was twisted three times on itself, though the ileum was not involved in the twist. The diverticulum was excised, its stump turned into the intestine by Lambert's sutures, and the patient recovered.

Obstruction by pressure of a distended diverticulum.—This is an extremely rare occurrence, for when the diverticulum is in its usual position with its distal extremity free in the peritoneal cavity, it would, if dilated and cyst-like, displace and not compress the intestinal coils. There is, however, a specimen in the

Museum of University College (preparation 1700) where a long diverticulum with a cyst-like extremity, measuring 7·5 c.m. by 5·5 c.m., had become wedged in Douglas' pouch in a woman æt. 19. A coil of small intestine had here become compressed between the diverticulum and the sacrum, and so had caused a fatal intestinal obstruction.

Invagination of Meckel's diverticulum.—This is a very important and interesting way in which the diverticulum may produce intestinal obstruction. Until a few years ago it was regarded as an occurrence of great rarity; indeed, fifteen years ago the preparation in our museum from the case described by Dr. Hilton Fagge seems to have been the only museum specimen in London. However, a number of cases have been recorded in recent years, and at the present time there are five preparations in the Gordon Museum of the various stages of invagination of the diverticulum, while three additional cases are recorded in the Clinical Reports.

Before describing invagination of the diverticulum and intussusception resulting from this, it may be noted that in two cases—38 and 39—both of the ileo-cæcal variety, a diverticulum was found joining the ileum just above the tumour. No connection between the presence of the diverticulum and the intussusception could be made out in either case, and its presence was probably a coincidence.

There is no doubt that occasionally the diverticulum may be invaginated into the ileum without causing an intussusception, or giving rise to any acute symptoms. When this occurs, owing to the obstruction to its blood supply, the wall of the diverticulum becomes œdematous and thickened, and it may eventually give rise to a polypoid structure, which owing to secondary changes may become so altered in appearance that the mode of formation of the polypus may not be at all obvious. Two preparations in the Gordon Museum illustrate this process. Specimen 834 is from a female patient, æt. 19, who was admitted for chronic dysentery. At the autopsy there were numerous polypi in the colon and rectum, but in addition to these there was in the ileum, two feet above the ileo-cæcal valve, a polypus the size of a cherry. The peritoneal coat of the intestine showed

in this situation a scarred and puckered appearance. Dr. Moxon suggested that this polypus was derived from an invaginated diverticulum. A still more interesting preparation (891) was found in a man, æt. 29, who had died of typhus fever (case 87). A club-shaped polypus is present in the ileum, which shows, especially at its dilated extremity, a fatty structure, though it is covered by normal mucous membrane. In the centre of the polypus is a narrow channel lined by peritoneum. When the serous coat of the ileum is examined there is seen a depression into which the central serous channel of the polypus opens. There can be no doubt that we have here an inverted diverticulum, nor can there be any doubt from its appearance that the inversion was of long standing. It appears not to have caused any symptoms.

Several cases have been recorded where a diverticulum has been found inverted and hanging in the lumen of the gut without having given rise to symptoms. Mitchell, in his series of cases quoted above, found an inverted diverticulum in a man æt. 41, who died of alcoholism, the diverticulum not having caused any symptoms. It was three inches long, one and a half inches in diameter, and situated thirty-six inches above the cæcum.

If a single polypoid mass is found in the ileum, the serous coat of the intestine should be carefully examined for any depression or appearance of scarring. Several cases of intussusception of the ileum have been described where a single polypoid tumour has been found at the apex. Morrison³² describes the case of a man, æt. 62, who for four months had suffered from chronic intestinal obstruction. A movable swelling was felt, which was thought to be a malignant growth. An intussusception was found, and this was excised. When examined, an elongated tumour was found at the apex of the intussusception attached to the free border of the intestine. There was a distinct pucker on the serous surface of the gut at its attachment, but the polypus, which was composed of connective tissue undergoing myxomatous change, showed no central channel. Dr. Coupland³³ describes a case where three inches of ileum had passed along the last six inches of the small intestine to the ileo-cæcal valve. At the apex

of the intussusception was a cylindrical polypoid mass the size of a little finger. No mention is made of any dimple on the peritoneal coat of the intestine, but the position and shape of this polypus suggests the possibility of it having originated in an inverted diverticulum ilei.

Case 43 is probably of a similar nature. Here a tumour, the size of a chestnut, composed of fibrous tissue, was found at the apex of an ileic intussusception in a woman *æt.* 42. The position of this tumour is very suggestive, since the intussusception, which was seven inches in length, was situated about three feet above the ileo-cæcal valve. The specimen is preserved in the Gordon Museum (preparation 1108).

Mr. Lockwood³⁴ describes a similar case, where the polypus was composed of fibrous and muscular tissue and contained a calcareous nodule.

Thus it is seen that the inverted diverticulum may form a polypus, which may later be the cause of an intussusception. It is of interest to note that the ages of these patients varied between 16 and 62. In case 43, in Morrison's case, and also in a somewhat similar case recorded by Lawford Knaggs,³⁵ the obstruction was chronic.

In other cases, at the apex of an intussusception there may be found an inverted diverticulum, the nature of which is obvious, both from its structure and the fact that the orifice of its inverted peritoneal coat is seen on the serous surface of the gut. In these cases the diverticulum is easily recognisable as such, though it is much swollen, and the mucous membrane covering it may show gangrenous areas.

There can be no doubt in these cases that the inversion is of recent occurrence, and that the diverticulum acts as a foreign body in the intestine, and, by causing excessive peristaltic action, thus produces the intussusception. This variety of intussusception usually occurs in children, the history is acute, and the symptoms are characteristic. Cases 38-42 are typical examples of this condition.

Dr. Zum Busch records a case where the patient was 21 years of age, where not only was the diverticulum invaginated, but

there was a fatty tumour at its apex. One would think that this combination of a tumour with a diverticulum would be especially liable to produce inversion, followed by an intussusception.

In case 40 the intussusception was multiple, which itself is a rare occurrence. The history is not quite typical for an intussusception, since the bowels had acted, and there was no blood passed per rectum, and no tumour was felt. Mr. Lane operated, and found an intussusception in the right iliac region. This was reduced, and was found to contain a second, which, in the same way, contained a third. When the last intussusception was reduced, it was found to contain an inverted diverticulum. This was reduced, its end was excised, and the intestine drained by a tube, which was tied into the diverticulum. T. Carwardine³⁶ records a case which is similar to this, in that three intussusceptions were present, while clinically no tumour could be felt. The inverted diverticulum soon becomes œdematous, as the result of its obstructed blood-supply, and its walls become very œdematous and thick. Patches of gangrene also soon appear on its mucous surface. A case is recorded by O'Connor³⁷ of sloughing of an intussusception, the patient passing the slough per anus and recovering. Examination of the slough showed that a Meckel's diverticulum was present in the intussusception.

Occasionally the walls of the diverticulum become so thick and œdematous that it is impossible to reduce it even by manipulation. There are two interesting specimens in the Gordon Museum, at present unmounted, which show this condition. One of these (preparation 03^{66a}), to which there is no history, shows a thick-walled diverticulum invaginated into the ileum, which from the condition of its walls would appear to have entered into the formation of an intussusception. The other (preparation 711S) appears to have been found at a post-mortem on a case of carcinoma of the sigmoid. Though the diverticulum has thick walls, the ileum into which it is invaginated has a perfectly normal appearance, and no symptoms resulted. In both these cases the diverticulum is much thickened, and the central peritoneal channel will only admit a small probe. In neither could the diverticulum have possibly been forced into its former position

by manipulation. Hence one finds that occasionally in treating these cases the intussusception is reduced, and then a hard body is felt within it which cannot be reduced. There are, then, two methods of treating the unreduced diverticulum which obviously must not be left *in situ*: (1) The intestine may be opened by a longitudinal incision and the diverticulum ligatured and removed, care being afterwards taken to securely close the depression in the serous intestinal coat where the invagination occurred. This mode of treatment was adopted in the case described by Mr. Rutherford Morrison mentioned above. (2) The portion of the intestine containing the diverticulum may be excised. This was done by Mr. Dobson,⁸⁸ who found that the diverticulum tore when he attempted to reduce it, and so he excised a piece of intestine with the inverted diverticulum. The patient, a boy aged four and a half years, recovered. Whichever method of treatment was adopted would depend chiefly on the condition of the bowel.

The specimen from case 49 is in the Gordon Museum, but unmounted (preparation S89). Here an intussusception, which had reached to within four inches of the anus, was easily reduced, except its last four inches. The ensheathing layer of this irreducible portion has been cut open, showing a thick-walled diverticulum about an inch long, forming the apex of the intussusception. In case 44 an intussusception had occurred a short distance above Meckel's diverticulum; instead of passing along the distal portion of the ileum, the intussusception was drawn on by its mesentery in such a way that it was directed into the diverticulum which it partly filled. This specimen is preserved in the museum (preparation 1095).

Injury of Meckel's diverticulum.—When the distal extremity is free in the peritoneal cavity the diverticulum is hardly likely to be injured, but when it is adherent, especially to the umbilicus, one can understand that it might be liable to injury.

Case 47 is possibly one of injury to the diverticulum, though it might be a case of strangulation of the ileum beneath a band formed by the diverticulum with subsequent sloughing of this process, the accident being thus merely a coincidence, or the blow

possibly forced the coil of intestine into its dangerous position. There was, however, a definite history of injury to the abdomen caused by a fall only two days before admission, no symptoms were present before this, and there was then a marked bruising in the right iliac region. On the other hand, semi-solid motions not containing any blood had been passed, and the diverticulum was found at the post-mortem to be inflamed and partially torn away from its attachment to the ileum. The case is described by Dr. Hilton Fagge in his paper³⁹ on intestinal obstruction, and he expresses no opinion as to the relation between the injury and the tear in the diverticulum.

In case 46, where the jejunum was ruptured as the result of a kick from a horse, an uninjured Meckel's diverticulum was present adherent throughout its whole length to the mesentery.

Strangulation by a "solitary band."—This band may doubtless be produced in a number of ways, but a frequent attachment to the root of the mesentery of the lower part of the ileum suggests that it may often be a persistent diverticular ligament, the diverticulum itself having completely disappeared.

Dr. Mahomed⁴⁰ describes a case where a fibrous band, extending from the umbilicus to the root of the mesentery in the right iliac fossa, had caused a fatal obstruction. Though no diverticulum was present there can be but little doubt as to the nature of this band.

Meckel's diverticulum and mesenteric cysts.—It has been shown that it is by no means uncommon for the diverticulum to have a large cyst-like distal extremity and a very narrow pedicle. That the cyst-like extremity may become completely separated from the ileum has been shown in describing umbilical cysts. A rare form of mesenteric cyst has unstriated muscular fibres in its wall, and internally may show mucous membrane with tubular glands. Histologically these cysts closely resemble small intestine. Though there is, so far as I am aware, no definite evidence that this is the case, one cannot help thinking that these cysts might be derived from a Meckel's diverticulum which has become detached and become adherent to the mesentery.

These cysts are discussed by Dr. Dowd,⁴¹ Mr. Eve,⁴² and Mr. Moynihan.⁴³

Strangulation of intestine through a slit in the mesentery.—In discussing the anatomy of the diverticulum, it has been pointed out that these apertures may be bounded by a fibrous cord, which is probably a diverticular ligament. The aperture is produced in these cases by absorption of that part of the mesentery adjacent to the cord. A coil of ileum may pass beneath this band through the aperture in the mesentery of the ileum, whereas in the ordinary strangulation beneath a diverticular band, the aperture is formed by an absorption of the mesentery of the diverticulum.

Sir Frederick Treves has pointed out, in the Hunterian Lectures for 1885, that in many cases this aperture is produced by absorption of the mesentery between the termination of the right colic artery and the last of the intestinal branches of the superior mesenteric.

Duplication of the intestine.—This very rare deformity is explained in many cases by Fitz (44) as the result of a persistent diverticulum. It may be pointed out here that in Bilton Pollard's case, where the diverticulum measured 86 inches in length, that the small intestine had the appearance of bifurcating at the point of origin of the diverticulum, and it was only possible, by tracing the lower ends to their attachment, to decide which was the lower end of the ileum and which was the diverticulum.

ABSTRACTS OF CASES FROM THE CLINICAL AND POST-MORTEM REPORTS OF GUY'S HOSPITAL.

CASE 1.—John C., æt. three months, was admitted in 1842 for fæcal fistula at the umbilicus. This closed after treatment by caustics. He subsequently died with intestinal obstruction. At the autopsy a diverticulum was found adherent to the umbilicus. The obstruction was caused by a band compressing the ileum just below the diverticulum. (See Guy's Hospital Reports, 1843, p. 470.)

CASE 2.—A male child, when eight days old, was treated for a "fungus" at the umbilicus. This was cauterised, and fæcal matter then commenced to ooze. Subsequently a few inches of intestine protruded during coughing. This eventually disappeared, though granulation tissue and fæcal discharge persisted. He died two years after of bronchitis, and at the autopsy a diverticulum three inches long was found passing from the ileum eighteen inches from the ileo-cæcal valve to the umbilicus, where it opened. (See Guy's Hospital Reports, 1843, p. 471.)

CASE 3.—Frederick C., æt. nine months, was admitted in 1904 for polypoid tumour at the umbilicus, which had recurred after cauterisation. Sir Alfred Fripp excised a diverticulum. The patient recovered. (See Sir Alfred Fripp's Surgical Reports, 1904, No. 155.)

CASE 4.—Frederick T., æt. 15 months, was admitted in 1904 for an umbilical polypus. This was removed, but in so doing a Meckel's diverticulum was opened. The peritoneal cavity was then opened and the diverticulum sewn up by means of Lembert's sutures. Next day a coil of intestine had protruded. This was replaced, but the child did not recover from the shock. (See Mr. Jacobson's Surgical Reports, 1904, No. 336.)

CASE 5.—Charles S., æt. 16, was admitted under Mr. Golding-Bird for an umbilical polypus. This was cut away with scissors and the wound plugged. Microscopically, the tumour was composed of fibrous and muscular tissue with typical Lieberkuhn's follicles, but no villi were present. (See Mr. Golding-Bird's Surgical Reports, 1895, No. 126.)

CASE 6.—Charles W., æt. four months, was admitted for a polypoid growth and fistula at the umbilicus. Sir Alfred Fripp made an incision to the left of the mid line, and found a Meckel's diverticulum adherent to the umbilicus. The diverticulum and polypus were excised, and the stump of the former was invaginated into the intestine. (See Sir Alfred Fripp's Surgical Reports, 1902, No. 62.)

CASE 7.—Herbert H., æt. 32, was admitted for a fæcal umbilical fistula, which had appeared ten days previously. He had previously enjoyed good health, and the œdema and discharge disappeared with the use of fomentations. The patient was discharged with instructions to come up again if he had any further trouble. Dr. Butler, of Beckenham, who sent him to the hospital, kindly writes to say that the man, who has now left the district, had, as far as he was aware, no further trouble. (See Mr. Golding-Bird's Surgical Reports, 1901, No. 446.)

CASE 8.—Gilbert M., *æt.* four weeks, was admitted for a tumour projecting at the umbilicus, where there had been a fæcal fistula since the separation of the umbilical cord. No motion had passed by the anus since the appearance of the tumour. At the autopsy there was an everted ring of mucous membrane at the umbilicus. From the centre of this a finger-like tumour presented. On opening the abdomen it was found that the distal part of the ileum had become invaginated, forming an intussusception which had travelled upwards, and had projected through the opening of a patent Meckel's diverticulum. A probe passed through the aperture of the central projection, passed into the empty distal part of the ileum. A probe between the intussusception and the everted mucous membrane, passed into the proximal dilated portion of the small intestine. (See Mr. Golding-Bird's *Surgical Reports*, 1895, No. 127, and *Path. Soc. Trans.*, 1895.)

CASE 9.—Samuel C., *æt.* 5, was admitted under Dr. Fawcett for acute intestinal obstruction of six days' duration. Mr. Steward operated, and found a flask-shaped diverticulum ilei three inches in length by one and a half inches in width, adherent at its distal extremity to the great omentum. The diverticulum was dark and gangrenous, and beneath it was a strangulated coil of intestine three feet in length. The diverticulum was excised, and two punctures, afterwards sewn up, were made in the distended bowel. The strangulated intestine was not gangrenous. The patient afterwards developed broncho-pneumonia, but eventually made a good recovery. (See *Clinical Reports*, 1903, No. 222.)

CASE 10.—Albert K., *æt.* 20, who had previously suffered from appendicitis, was admitted for pain in the left iliac fossa, vomiting and constipation. Mr. Steward operated, and found old adhesions in the right iliac fossa. A Meckel's diverticulum was found directed towards the right iliac fossa in a sloughing condition, and perforation had occurred. The diverticulum was excised and its base sutured, and this part of the intestine was left in the abdominal wound. At the autopsy there was general peritonitis. No recent appendicitis was found, and the condition of the diverticulum was attributed to it having been compressed beneath a band, the result of old peritonitis. (See *Inspections*, 1902, No. 360, and *Clinical Reports*, 1902, No. 527.)

CASE 11.—Geo. D., *æt.* 17, was admitted under Dr. Washbourn for abdominal pain, vomiting and constipation. Laparotomy was performed, and peritonitis found, with matting of the intestines. A deeply-congested loop of intestine was left in the wound, which was drained. At the autopsy a Meckel's diverticulum was found two feet from the ileo-cæcal valve, and two inches below the coil of intestine found in the wound. The ileum below it was collapsed. The mucous membrane, both of the appendix and also of the diverticulum, was normal. The cause of the peritonitis was doubtful. (See *Inspections*, 1897, No. 334.)

CASE 12.—Harry B., *æt.* 12, was admitted under Dr. Hale White for abdominal pain, vomiting and constipation. The symptoms had commenced six days before, shortly after eating six raw green apples. The core of an apple was found on one occasion in the vomit. He died six days after admission, and at the autopsy a diverticulum ilei was found in a sloughing condition. There were many peritoneal adhesions around this, and a coil of intestine was found to have slipped through an aperture in these, and the bowel below was empty and collapsed. The case was regarded as one of

primary inflammation of the diverticulum with peritonitis and secondary obstruction beneath the adhesions this produced. (See Inspections, 1887, No. 284.)

CASE 13.—Bertha F., æt. 26, was admitted under Sir Cooper Perry for phthisis. At the autopsy there was tuberculous ulceration of the ileo-cæcal valve, and a Meckel's diverticulum was present, in the wall of which were four chronic tuberculous ulcers. (See Inspection, 1890, No. 426.)

CASE 14.—Geo. B., æt. 35, was admitted for phthisis under Dr. Taylor. At the autopsy a Meckel's diverticulum was found three feet above the ileo-cæcal valve, at the orifice of which was a small tuberculous ulcer. (See Inspection, 1902, No. 103.)

CASE 15.—Wm. F., æt. 19, was admitted under Dr. Taylor for phthisis and tuberculous meningitis. At the autopsy there was extensive tuberculous ulceration of both the small and large intestine, and tuberculous ulcers were also present in a short Meckel's diverticulum. (See Inspection, 1898, No. 242.)

CASE 16.—Alfred Tait, æt. 60, was admitted under Mr. Bryant for hypertrophy of the prostate, vesical calculi, and cystitis. At the autopsy a wide diverticulum was found springing from the ileum two feet above the ileo-cæcal valve. From it a small fibrous cord ran to the mesentery close to the cæcum. This formed a loop which passed over the ileum between the ileo-cæcal valve and the point of origin of the diverticulum. The band caused no symptoms. (See Inspection, 1885, No. 83.)

CASE 17.—Wm. B., æt. 17, was admitted in a moribund condition in 1868, with two days' history of acute intestinal obstruction. At the autopsy a diverticulum was found two feet from the ileo-cæcal valve, the distal extremity of which was attached to the mesentery. Nearly all the small intestine had passed beneath this band, but it was, however, easily withdrawn. (See Dr. Hilton Fagge, Guy's Hospital Reports, 1868, p. 359.)

CASE 18.—Charles S., æt. 18, was admitted for acute intestinal obstruction and died the following day. At the autopsy a diverticulum was found arising by a narrow pedicle about six inches from the ileo-cæcal valve. From the fundus of this a narrow cord passed to the mesentery, and beneath the loop thus formed three feet of the ileum were strangulated and almost gangrenous. (See Dr. Hilton Fagge, Guy's Hospital Reports, 1868, p. 361.)

CASE 19.—Elizabeth W., æt. 10, was admitted under Dr. Wilks for symptoms of intestinal obstruction of nine days' duration. At the autopsy a diverticulum four inches in length was found, which was pervious and attached to the umbilicus, the band was bent over towards the mesentery, thus obstructing the bowel." (See Inspection, 1864, No. 193, and Museum preparation, 1060.)

CASE 20.—William C., æt. 19, was admitted under Dr. Pye-Smith for acute intestinal obstruction. At the autopsy a long and wide diverticulum was found arising from the ileum a few inches above the ileo-cæcal valve, and attached by means of a thin fibrous cord to the mesentery. A coil of the ileum had become strangulated beneath this loop. The strangulated knuckle of gut, and the base of the diverticulum, were both in a sloughing condition. (See Inspection, 1886, No. 66.)

CASE 21.—Samuel P., æt. 9, was admitted under Dr. Perry for symptoms of intestinal obstruction, and a swelling in the right iliac fossa. A diagnosis of appendicitis was made. At the autopsy a diverticulum was found nine

inches from the ileo-cæcal valve, from its extremity a tough fibrous cord passed to the mesentery of the lower end of the ileum. Beneath this band eight inches of ileum, below the point of attachment of the diverticulum, had slipped and become strangled. The cord had also passed across the base of the diverticulum, which was inflamed and covered with lymph. The bowel was in a recoverable condition. (See Inspection, 1893, No. 223.)

CASE 22.—John L., æt. 40, was admitted under Dr. Bright in 1829 for acute intestinal obstruction. At the autopsy a diverticulum the size of a hen's egg was found, from which a fibrous band passed to the mesentery. A portion of the ileum below the diverticulum was strangled by the band, and general peritonitis was present. (See Dr. Fagge, *Guy's Hospital Reports*, 1868, p. 363.)

CASE 23.—Frank F., æt. 24, was admitted under Dr. Taylor for acute intestinal obstruction. There was a history of a severe attack of colic a year previously, followed by two or three slighter attacks. At the operation a Meckel's diverticulum was found adherent by a fibrous cord to the umbilicus. This was divided, and a tube was tied in the dilated intestine. At the autopsy general suppurative peritonitis was found. The ileum had been opened and drained six inches above the valve. (See Inspection, 1899, No. 154.)

CASE 24.—Elizabeth W., æt. 10, commenced to vomit after eating some gooseberries, and this was followed later by constipation. She then developed all the symptoms of acute peritonitis. At the autopsy a band was found passing from about eighteen inches above the ileo-cæcal valve to the umbilicus. The diverticulum was patent throughout its whole length, and at its proximal end was the size of the gut. The intestine below the diverticulum had passed over the band, and was coiled and hanging down in the pelvis. On manipulating the parts, laceration occurred at the intestinal attachment of the diverticulum. Separation was probably beginning here during life. (See Dr. Fagge, *Guy's Hospital Reports*, 1868, p. 363.)

CASE 25.—Geo. B., a porter, was admitted to St. George's Infirmary with symptoms of acute intestinal obstruction of fifteen hours' duration. An ill-defined swelling was found extending from the right iliac region to the umbilicus. At the autopsy a long diverticulum was found springing from the ileum, thirty inches above the ileo-cæcal valve. This surrounded a loop of ileum two and a half feet in length, and its distal extremity was fixed to the mesentery between its own proximal attachment and the strangulated bowel. The coil of ileum affected was that immediately above the origin of the diverticulum. (See *Guy's Hospital Gazette*, vol. 7, p. 183, and *Museum Preparations*, 1063.)

CASE 26.—From a patient admitted under Sir Wm. Gull, who died of intestinal obstruction. From the apex of a diverticulum three inches in length a fibrous cord passes to the mesentery. Beneath this a coil of intestine was strangulated. (*Museum Preparations*, 1061.)

CASE 27.—Wm. B., æt. 15, was admitted under Dr. Moxon for acute intestinal obstruction. He died on the tenth day of his illness, and at the autopsy a fibrous cord was found passing from a Meckel's diverticulum to the mesentery, forming a loop, through which a coil of ileum had slipped. The diverticulum contained a concretion the size of a cherry-stone composed of skins of fruits.

CASE 28.—Frances C., æt. 41, was admitted for symptoms of acute intestinal obstruction. She was operated on by Mr. Bryant, but the symptoms persisted. At the autopsy a loop of ileum eight inches in length was found strangulated beneath a band, which stretched from the small intestine to the broad ligament. (See Inspections, 1873, No. 18.)

CASE 29.—Herbert P., æt. four months, was admitted for an inflamed and irreducible left inguinal hernia. At the autopsy the coils of intestine in the left inguinal region were found matted together and adherent to the sac, which also contained omentum and the end of a diverticulum ilei two inches long given off twelve inches from the ileo-cæcal valve. The bowel was slightly kinked at this spot. (See Inspection, 1888, No. 108.)

CASE 30.—Mary F., æt. 49, was admitted under Mr. Howse for a strangulated left femoral hernia. Herniotomy was performed, and the patient died three days later. At the autopsy a diverticulum was found, the globular extremity of which had been contained within the hernial sac. From the side of the diverticulum a fibrous band passed to the mesentery close to the origin of the diverticulum. A coil of intestine had passed beneath this loop, but showed no sign of strangulation. (See Inspection, 1884, No. 418, and Museum Preparation, 1065.)

CASE 31.—Henry W., æt. 37, was admitted for a strangulated femoral hernia, which was found to contain sloughing omentum, which was excised, but the patient died the next day. At the autopsy there was a very large diverticulum ilei, from the side of which a fibrous band passed to the root of the mesentery. A coil of ileum was found beneath this arch, but was not strangulated. (See Inspection, 1874, No. 13.)

CASE 32.—Francis H., æt. 46, was admitted for cirrhosis of the liver. At the autopsy an old right inguinal hernia was found, which, in addition to small intestine, contained a Meckel's diverticulum, which was adherent to the sac. (See Inspections, 1877, No. 448.)

CASE 33.—A male infant survived birth three days, during which time he constantly vomited. The intestine preserved in the museum shows occlusion of the bowel at two points, one four inches and the other sixteen inches above the ileo-cæcal valve. From the ends of the bowel fibrous cords pass which are connected with one another by a mesentery. (See Museum Preparation, 771.)

CASE 35.—Isabella P., æt. six days, was admitted under Mr. Davies Colley for constant vomiting and constipation. An artificial anus was made, but the child died in two days. At the autopsy a membranous diaphragm was found completely occluding the ileum nine inches from the cæcum. (See Inspection, 1877, No. 317, and Museum Preparation, 770.)

CASE 36.—Jane T., æt. 19, was admitted under Mr. Durham for chronic dysentery. Death was due to exhaustion, and at the autopsy a sessile polypus the size of a cherry was found in the ileum two feet above the ileo-cæcal valve. The serous surface of the intestine was puckered at this spot. Polypi were also present in the colon and rectum. (See Inspection, 1885, No. 87.)

CASE 37.—Alfred H., æt. 29, died of typhus fever in 1854. At the autopsy a polypus was found in the ileum, the surface of which was covered by mucous membrane. The polypus was composed chiefly of fatty tissue. A depression from the peritoneal covering of the gut leads into a smooth space in the long axis of the polypus. (See Inspection, vol. 37, p. 382.)

CASE 38.—Edward A., æt. 5 months, was admitted with the usual signs and history of intussusception. At the autopsy a large diverticulum ilei was present one foot from the ileo-cæcal valve. This was situated above the intussusception, which was of the ileo-cæcal variety, and apparently had no connection with it. (See Inspection, 1885, No. 20.)

CASE 39.—Geo. S., æt. 4 months, was admitted with a typical history of intussusception. At the autopsy an ileic intussusception was found. Two inches above this was a diverticulum ilei which had apparently had nothing to do with it. (See Inspection, 1896, No. 267.)

CASE 40.—Percy W., æt. 16 months, was admitted under Dr. Goodhart for vomiting and diarrhoea; no tumour could be felt. Mr. Lane operated and found an intussusception in the right iliac region. This was reduced, and was found to contain a second, which in the same manner contained a third. The last intussusception contained an inverted diverticulum, the end of which was removed and a tube tied in the stump to drain the distended gut. At the autopsy the intestine was dark and congested for fourteen inches above and ten inches below the diverticulum. (See Inspection, 1896, No. 56.)

CASE 41.—Alfred L., æt. 11 months, was admitted under Dr. Hale White with a typical history of intussusception. The tumour disappeared on inflation with milk, but the child died later in the same day. At the autopsy an ileic intussusception was found, which on attempting reduction ruptured. The terminal part of the invaginated bowel was found to contain an inverted diverticulum three c.m. in length, which was congested and much thickened. (See Inspection, 1902, No. 463.)

CASE 42.—Wm. B., æt. 16, was admitted under Mr. Dunn for acute intestinal obstruction of five days' duration. Laparotomy was performed and a gangrenous ileic intussusception was found. This was excised, but the patient died shortly after. When the resected gut was examined a small inverted Meckel's diverticulum was found. (See Inspection, 1902, No. 414.)

CASE 43.—Hannah K., æt. 42, was admitted under Dr. Moxon for chronic intestinal obstruction. She died five weeks later, and at the autopsy an ileic intussusception was found, at the apex of which was a polypus the size of a chestnut. The tumour, which was superficially ulcerated, was composed of fibrous tissue. The intussusception was situated three feet above the ileo-cæcal valve. (See Inspection, 1879, No. 88, and Museum preparation, 1108.)

CASE 44.—Eliz. N., æt. 16, was admitted for a deformed toe. While in the hospital she developed symptoms of sub-acute intestinal obstruction. At the autopsy an ileic intussusception was found, at the apex of which was a diverticulum. The intussusception had extended as far as and had partially filled the diverticulum. (See Inspection, 1867, No. 467.)

CASE 45.—James C., æt. 22, was admitted under Dr. Fagge for acute intestinal obstruction of five days' duration. Laparotomy was performed, and the intussusception reduced, but the patient died shortly after. At the apex of the intussusception a short inverted diverticulum was found. (See Inspection, 1874, No. 173, and Museum preparation, 1107.)

CASE 46.—Charles S., æt. 40, was admitted for an abdominal injury caused by a kick. At the autopsy general peritonitis was present, and the jejunum was ruptured. A large Meckel's diverticulum was present adherent to the mesentery throughout its whole length. (See Inspection, 1877, No. 231.)

CASE 47.—Edward G. was admitted with symptoms of peritonitis following on an abdominal injury caused by a fall on a heap of stones. On admission there was a bruise in the right iliac region, which later on became more marked. At the autopsy a diverticulum of the ileum was found, from which a band passed to the mesentery. Beneath this a coil of intestine passed, but the diverticulum was inflamed and partially torn away from its attachment to the ileum. (See Inspection, 1867, No. 197.)

CASE 48.—A child, æt. 2, was admitted into the Shadwell Hospital under Mr. Dunn in 1902 with a history of six days' obstruction, but no blood or mucus had been passed. Laparotomy was performed, and a retrograde intussusception was found a short distance above the cæcum. The ensheathing layer was sloughing, and the intussusception was excised. The child died forty-eight hours later, and at the autopsy there was no peritonitis and no yielding of the stitches. (See Museum Preparation, O2²⁸.)

CASE 49.—Ethel C., æt. 5 months, was admitted under Sir Cooper Perry with a typical history of intussusception of five days' duration. The tumour could be felt per rectum, and an attempt was made to inflate under an anæsthetic, but the child became very bad, and died the following day. At the autopsy an intussusception was found, the apex of which was only four inches from the anus. It was found possible to reduce the intussusception by traction, except the last four inches. On opening the ensheathing layer, an inverted Meckel's diverticulum the size of the terminal phalanx of the little finger was found at the apex of the intussusception. This had passed through the ileo-cæcal valve, and was then about three inches beyond it. (See Inspection, 1897, No. 80.)

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THE PLATINOCHLORIDE TEST FOR CHOLINE IN HUMAN BLOOD.

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INTRODUCTION.

HALLIBURTON and Mott have recently published^{1,2} extensive researches on the chemistry of nerve degeneration; and from the fact that lecithin, an important constituent of nerve tissue, may be broken up into choline and glycerophosphoric acid, they inferred that chlorine would appear in recognisable quantities in the circulating fluids of persons in whom nerve degeneration was taking place. To investigate the possible presence of this substance in blood and cerebro-spinal fluid they employed, among other tests, that with platinum chloride.

The details of this test will be found in an article by Mott.³ The principle is to extract the blood several times in succession with absolute alcohol, in the belief that the choline will thereby be freed from potassium, to precipitate the choline as choline platinochloride, and to crystallise the latter from 15 per cent. alcoholic solution. The crystals are yellow octahedra, readily seen under the low power of the microscope.

In confirmation of this test, Halliburton and Mott examined other properties of the crystals, and also observed the physiological action of the material they extracted from the blood and

cerebro-spinal fluid. Upon these points the present authors have not touched; their desire was merely to test the clinical value of the platinum chloride reaction.

METHOD USED IN THE PRESENT RESEARCH.

An attempt was made to obtain comparable results in all the experiments by using, as far as possible, the same volumes of solvent at the corresponding stages of the process. The full method is as follows:—

Sixty minims, or about 4 c.c., of blood were drawn from the vein of the patient and injected into 30 c.c. of absolute alcohol. The mixture was allowed to stand for half an hour, being stirred from time to time. It was then filtered. The pale yellow filtrate was evaporated at 40° C. When dry, the residue was rubbed up with 7 c.c. absolute alcohol and filtered; there was always a yellowish-brown insoluble deposit, which was washed with a further 3 c.c. absolute alcohol, a total of 10 c.c. being thus used for the extraction. The filtrate was evaporated to dryness at 40° C. This step was twice repeated. The dry residue was then rubbed up with 7 c.c. absolute alcohol, filtered, and the gummy residue further washed with 3 c.c. absolute alcohol. To the filtrate at least five drops of a 10 per cent. solution of pure platinum chloride in absolute alcohol were added, and the turbid mixture evaporated at 40° C. The yellow-brown residue was rubbed up with 7 c.c. absolute alcohol to redissolve the excess of platinum chloride; the mixture was filtered, and the residue washed with 3 c.c. absolute alcohol. There were thus obtained:—

1. *A filtrate*:—This, which throughout the paper is referred to as the “final filtrate,” contains the excess of platinum chloride, and those double platinochlorides, which are the more soluble in absolute alcohol. It was evaporated to dryness at 40° C., redissolved in 3 c.c. absolute alcohol, filtered and set to crystallise spontaneously. Crystals obtained from it we term “crystals from the final filtrate.”

2. *A residue*:—This, which we refer to as the “final residue,” contains the less soluble double platinochlorides. Amongst these would be that of choline. This residue was washed three times

with the same 3 c.c. of 15 per cent. alcohol in distilled water. The double platinochlorides, insoluble in the absolute alcohol, but now dissolved in 15 per cent. spirit, were evaporated to dryness at 40° C., redissolved in 3 c.c. of 15 per cent. spirit, filtered, and allowed to crystallise spontaneously. Crystals so obtained we term "crystals from the final residue," and amongst them would be those of choline, were any originally present in the blood. The absolute alcohol employed throughout had a strength of 99.6 per cent., in order to take up as little of the inorganic salts in the blood as possible; the importance of this has been well pointed out by numerous observers.³

RESULTS OF APPLYING THE TEST TO HUMAN BLOOD IN HEALTH AND DISEASE.

Mott states that the yellow octahedral crystals are obtainable from 5 c.c. or less of blood from persons in whom active nerve tissue destruction is taking place; whereas "using 10 c.c. of normal human blood the results are practically negative, although frequently a few small octahedra may be found on careful examination."⁸ From a clinical point of view this would be of great value in diagnosis, and we proceeded to test it.

Typical crystals were readily obtained from 60 minims of the blood of four male patients suffering from general paralysis of the insane, three male and two female patients suffering from locomotor ataxia, two male patients suffering from disseminated sclerosis, two male patients suffering from compression myelitis, one male patient suffering from lateral sclerosis of the cord, one female patient suffering from chorea, and from one male patient suffering from combined scleroses of the cord.

On testing perfectly healthy persons in the same way, however, yellow octahedral crystals were obtained with equal facility. This was so in the case of each of the authors of this paper and of three robust medical students. At first we hoped that, in cases of nervous degeneration, there would be more abundant crystals than in normal subjects; but even of this we could not convince ourselves. Two of the healthy students yielded as

plentiful a crop of typical yellow octahedral crystals as did any one of the patients suffering from nervous disease.

Sources of Fallacy in the Test.—The results just described suggested that there was some fallacy in the test. From further investigations we conclude that some of the yellow octahedral crystals consist of an inorganic platinochloride, probably the double chloride of platinum and potassium.

Incineration.—The experiments from which we draw this conclusion are those in which we incinerated the alcoholic extract of the blood.

Four c.c. of blood were taken, extracted with 30 c.c. absolute alcohol; dried; and extracted with 10 c.c. absolute alcohol as exactly in the process already detailed; re-extracted with 10 c.c. absolute alcohol a second and a third time. The dried residue from this last extraction was then incinerated at a red heat for fifteen minutes, after which it was extracted with 10 c.c. absolute alcohol; platinum chloride solution was added, and the last steps of the process continued exactly as if no incineration had been done. From the final residue quantities of typical yellow octahedral crystals were obtained on every occasion.

We think the numbers of crystals were fewer than those given by the same patient's blood without incineration; but that crystals were obtained at all, showed that at least some of the crystals obtained by the test are not those of choline.

Swale Vincent¹⁰ expresses his opinion that the octahedra obtained by the "choline test" are due to ammonium-platinochloride; but that this is not entirely the case is also proved by the above experiments, for incineration must have destroyed both choline and ammonia. Control experiments with pure choline and with ammonium chloride gave no crystals after incineration.

It is necessary, therefore, to consider what are the inorganic salts of the blood. It contains normally⁹:—

Sodium	0.185 per cent.
Potassium	0.182 "
Calcium as oxide) in pig (...	0.014 "
Magnesium as oxide		0.098 "
Iron	0.059 "
Ammonia	0.003 "

The double platinochlorides of all these can form yellow octahedra distinguishable with difficulty under the microscope from those of the choline salt. We therefore took a minute quantity of the chloride of each separately and carried it through the "choline process," with the following results:—With the chlorides of sodium, calcium, magnesium, and iron the "final filtrate" yielded on crystallisation some yellow octahedra, while the "final residue" gave none.

Hence the solubility of the platinochloride of each of these in absolute alcohol is such that none of the salt remains to yield crystals in the "final residue." With the chlorides of potassium and ammonium the "final filtrate" gave a few yellow octahedra, while the "final residue" showed many such crystals. Hence not only are these chlorides sufficiently soluble in absolute alcohol to be carried on to the final stage of the extraction, but their double platinochlorides are so little soluble in absolute alcohol that much of them remains to form crystals in the "final residue." It is these which, in our opinion, vitiate the process as a reliable test for choline in the blood.

To complete the control experiments we carried a specimen of pure choline through exactly the same procedure, and found—

In the "final filtrate" abundance of needles due to excess of platinum chloride, and a considerable number of yellow octahedral crystals.	}	In the "final residue" many octahedral crystals.

Therefore choline remains in the "final residue" in the "choline process," but its platinochloride is not so insoluble in absolute alcohol but that some of it is removed in the "final filtrate." Indeed, we thought that the proportion of octahedral crystals in the "final filtrate" and "final residue" respectively

suggested that the solubilities of the double platinochlorides in absolute alcohol were as follow:—

Sodium platinochloride ...	} So soluble in absolute alcohol that all the octahedra were in the "final filtrate"; none were in the "final residue."
Calcium platinochloride ...	
Magnesium platinochloride ...	
Iron platinochloride ...	
Choline platinochloride ...	} Not so insoluble in absolute alcohol but that many octahedra appeared in the "final filtrate," though many also remained in the "final residue."
Potassium platinochloride ...	} Even less soluble in absolute alcohol than is choline platinochloride, so that though some octahedra appeared in the "final filtrate," more appeared in the "final residue."
Ammonium platinochloride ...	

It may be pointed out that although potassium chloride is usually said to be insoluble in absolute alcohol, 100 parts of the latter can dissolve 0.034 parts of this salt at 19° C.¹

Now 4 c.c. of normal blood contain 0.014 gm. of potassium chloride, and 10 c.c. of absolute alcohol—the amount used in extracting each residue—can dissolve 0.0034 gm., which corresponds to 0.011 gm. of potassium platinochloride. This would require 133 c.c. of absolute alcohol for solution.¹ The 10 c.c. actually used for washing the precipitate will therefore leave much of the potassium platinochloride to appear in the "final crystallate."

CONCLUSIONS.

From our experiments we conclude therefore—

1. That the obtaining of yellow octahedral crystals from blood by the platinochloride test is not of itself sufficient proof of the presence of choline.
2. That when 4 c.c. of blood are taken and carried through the "choline process," yellow octahedral crystals are obtained as readily from the blood of some healthy persons as from that of the subjects of various nervous disorders.

3. That of a mixture of choline, potassium, ammonium, sodium, calcium, magnesium, and iron chlorides, the first three alone will appear as yellow octahedra in the final stage.

4. That yellow octahedral crystals may be obtained from blood even after incineration, and that these are the platinochloride of potassium.

Finally, it may be pointed out that these experiments were performed upon blood alone. Donath² has affirmed the presence of choline in the cerebro-spinal fluid of epileptics and of those suffering from various acute nervous disorders. Upon this point we can venture to express no opinion. The crystals figured in the paper referred to have not, however, the shape characteristic of choline platinochloride.

We wish to thank Dr. Pembrey for the facilities which he afforded us in carrying out our work, a preliminary account of which was given to a meeting of the Physiological Society in November, 1903. We also thank Professor Halliburton and Dr. Mott for criticisms and suggestions upon further work on choline in human blood. The expenses were defrayed by a grant from the Royal Society to Dr. Pembrey.

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SOME OBSERVATIONS ON THE EFFECTS PRODUCED BY CHOLINE UPON ANIMALS.

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HALLIBURTON and Mott have noticed that choline has a characteristic physiological action when injected into the veins of animals, a marked lowering of blood-pressure being rapidly produced. This effect is either prevented or abolished, as the case may be, by the previous or subsequent injection of atropin.

Donath has asserted that a definite convulsive action is also produced upon the higher nerve centres, and has therefore concluded that it is an important factor in the production of the convulsions associated with epilepsy and general paralysis of the insane. He fails, however, to throw any light upon the question as to why there are no convulsions in other affections, such as disseminated sclerosis, diphtheritic paralysis, and tabes dorsalis, in which choline is also said to be present in the blood. Donath is probably wrong in the supposition that there is any excess of choline in the blood in epilepsy; if so, it can hardly be a factor in the production of the convulsions characteristic of that disease.

We have endeavoured to confirm Donath's experimental results, and also to learn the effect upon healthy animals of maintaining in their circulation for different periods various amounts of choline, and have used rabbits and rats for our experiments.

The rabbits are denoted A, B, C, D, each weighing about 700 grams, and being about three months old at the beginning of the experiments. Of the rats A, B, C, A and C weighed 120 grams, and were about six weeks old; B weighed 260 grams, and was about six months old.

The rabbits B, C, and the rat B were trephined and injected sub-durally, the rabbits A and D were injected intravenously, and the rats A and C intraperitoneally. The tables contain a record of the actual injections performed on the various animals.

We are greatly indebted to Dr. J. W. H. Eyre, who made the injections for us.

Rabbit A.—Injected intravenously with 1 per cent. choline in 0·75 per cent. sodium chloride solution; later with 2 per cent. choline in a similar solution.

Day of Experiment.	Dose given.	Total Dose received.
1st day	·3 c.c. 1 per cent. sol.	·003 gram.
3rd "	·4 "	·007 "
6th "	·5 "	·012 "
8th "	1·0 "	·022 "
10th "	1·0 "	·032 "
12th "	1·0 "	·042 "
14th "	1·0 "	·052 "
16th "	1·3 "	·065 "
18th "	1·0 c.c. 2 per cent. sol.	·085 "
23rd "	1·0 "	·105 "
26th "	1·0 "	·125 "
28th "	1·0 "	·145 "
30th "	1·0 "	·165 "
34th "	2·0 "	·205 "
38th "	1·5 "	·235 "
42nd "	2·0 "	·275 "
50th "	3·5 "	·345 "
54th "	3·5 "	·415 "
59th "	2·0 "	·455 "
62nd "	3·5 "	·525 "
66th "	3·5 "	·595 "
76th "	4·0 "	·675 "
80th "	—Death.	

In the case of this animal no clinical effects were noticed until the 12th day, when diarrhoea appeared; this became rather more acute for about three weeks and persisted until the end.

About the 30th day, when the animal had received a total dose of .2 gram of the drug, it became dull and listless, the forelegs were bowed outwards, while the hind legs were kept widely separated on standing up. The effect of the injection on the 50th day of the large dose of .07 gram was to produce profuse salivation almost immediately. By this time the changes first noticed about the 30th day were much more pronounced, so that the animal could no longer stand upright, but assumed a peculiar crouching attitude. On skiagraphing the animal the wrist joints of the forelegs were seen to be almost completely dislocated. After this, the first large dose, the animal was very tottery for some time, but later doses had less effect. On the 75th day the general condition of the animal was distinctly bad; diarrhoea and marked exophthalmos were present; the forelimbs seemed to have lost almost all power, the chest nearly touched the ground.

The injection of .08 gram on the 76th day produced marked salivation, and within five seconds slight convulsions came on and persisted for about fifteen seconds; next day it seemed fairly well, but four days later it died, *i.e.*, on the 80th day of the experiment.

Post-mortem, nothing abnormal was to be seen in any of the organs, except some slight hypertrophy and dilatation of the heart.

A microscopic examination of the various viscera and central nervous system was made.

The condition of the joints was such as is not uncommonly seen in rabbits kept in confinement, and cannot be attributed to the choline.

Liver.—Hepatic cells healthy on the whole, although they presented some slight cloudiness. The vessels were generally injected and there was some cellular exudation around the interlobular veins and bile capillaries.

Kidneys.—Slight cloudy swelling of cells of convoluted tubules. In other respects normal.

Stomach and Intestines.—Healthy.

Heart Muscle.—Showed no change.

Lungs.—Some scattered foci of broncho-pneumonia.

NERVOUS SYSTEM.

Nissl Method.—A large number of sections from the cerebral cortex, from the mesencephalon, and from various levels of the spinal cord were examined by this method. The cells in all these regions showed absolutely no changes from the normal. There was no evidence of any pathological condition in the meninges, ependyma, or vessels, which were also examined in sections stained with hæmatomylin and eosin.

Weigert-Pal Method.—Sections of the cerebral cortex, mesencephalon, pons, medulla, and cord were normal in every respect.

Busch Method.—Sections from the cortex, mesencephalon, and medulla showed no changes. Sections from the thoracic cord presented diffuse but slight degeneration in the lateral, and to a less extent in the posterior columns. This was much less marked in the cervical region and was absent in the post-thoracic segments.

Summary.—The slight changes present in some of the viscera and in the white matter of the thoracic cord were probably due in part to malnutrition associated with the rachitic condition, and in part to the effect of choline in the process of excretion.

Rabbit B.—Sub-dural injection with 1 per cent. and later with 2 per cent. choline solutions.

Day of Experiment.	Dose given.	Total Dose received.
1st day	0·2 c.c. 1 per cent. sol.	·002 gram.
6th "	0·5 "	·007 "
9th "	0·5 "	·012 "
12th "	·8 "	·02 "
14th "	·5 c.c. 2 per cent. sol.	·03 "
16th "	·5 "	·04 "
19th "	1·0 "	·06 "
24th "	1·0 "	·08 "
26th "	1·0 "	·10 "
28th "	·7 "	·114 "
30th "	·7 "	·128 "

On the 30th day the animal jerked its head violently at the moment of injection, with the result that the needle was driven back towards the cerebellum, its track being clearly seen after death. The animal was at once violently convulsed, nystagmus was very marked, violent circus movements were performed, and there was great retraction of the head. Four hours later, as the condition had not improved, chloroform was given and the animal killed. Post-mortem, the appearance of the viscera was normal, but a microscopic examination was also made. The convulsions were probably due in the main to the action of the choline, possibly also in part to the stimulation by the needle.

Clinical Symptoms in B.—As in the case of A, diarrhoea appeared about the 10th day. On the 12th day the animal jerked its head, and the needle entered the brain substance in the leg area, as shown by slight paralysis of the left leg, which cleared up completely ten days later. During this time intravenous injections were done instead of sub-dural ones, which were then resumed. After the injection on the 26th day the animal was very sluggish in its movements, and almost comatose for a short time (due to heart failure); it sweated profusely, and salivation was marked.

No fresh symptoms developed up to the time of the final injection.

HISTOLOGICAL EXAMINATION.

Nissl Method.—Sections from cortex and spinal cord showed no abnormalities.

Busch Method.—The cortex, pons, mesencephalon, medulla, and cord were examined, but the thoracic region of the latter was the only part to show any change. As in rabbit A, there was diffuse degeneration in the antero-lateral and posterior columns. This was more intense than in the previous animal, but never so marked as is seen resulting from gross experimental lesions; in other words, it had the appearance of being due to a slight toxic influence, and not that which is associated with Wallerian degeneration.

The adrenals, the spleen, and the kidneys were also examined, but with the exception of some slight cloudy swelling in the latter were not noticeably altered.

Rabbit C was injected sub-durally at the same times as rabbit B, with equal volumes of normal saline solution as a control, but never presented any symptoms.

Rabbit D.—In the case of rabbits A and B, small doses were employed at first and slowly increased, the experiments extending over a considerable period of time (30 and 80 days). The effect of an initial large dose was now tried.

3·5 c.c. of a 2 per cent. solution were injected into a vein. No convulsions were produced, but the animal was profoundly affected. Salivation was very marked, the animal trembled and became very tottery, and sweated profusely; in the course of an hour it had completely recovered.

Three days later a like dose was again given, without, however, producing similar symptoms.

Six days after the second injection the animal died, after having had severe diarrhœa for three days.

As we did not obtain the body until two days after death, no post-mortem examination was made.

Rat A (a control rat of the same brood was kept).—As the dose employed in the case of the rabbits had produced such slight symptoms, and the drug evidently was not highly toxic, relatively enormous doses were employed in the rats in order to see if any further symptoms could be obtained. The injections were made into the peritoneal cavity.

Day of Experiment.	Dose given.	Total Dose received.
1st day	1·0 c.c. 2 per cent. sol.	·020 gram.
5th "	1·3 "	·046 "
8th "	1·5 "	·076 "
11th "	1·5 "	·106 "
15th "	1·5 "	·136 "
18th "	1·5 "	·166 "
22nd "	1·5 "	·196 "
33rd "	1·5 "	·226 "
36th "	1·5 "	·256 "
40th "	1·5 "	·286 "
44th "	1·5 "	·316 "

Day of Experiment.	Dose given.	Total Dose received.
48th day.	1·0 c.c. 4 per cent. sol.	·356 gram.
52nd "	1·0 "	·396 "
55th "	1·25 "	·446 "
58th "	1·25 "	·496 "
61st "	1·25 "	·546 "
64th "	1·25 "	·596 "
69th "	1·0 c.c. 10 per cent. sol.	·696 "

Death.

Clinical Symptoms.—About the 8th day diarrhœa appeared, but no other effect was produced until the large dose on the 69th day was given, when the heart beat almost instantly became irregular and very feeble, and in two or three minutes the respirations assumed a Cheyne-Stokes character. Salivation and lachrymation were marked. In five minutes the animal became convulsed, and expired two or three minutes later.

Post-mortem.—All the viscera and peritoneum seemed quite healthy. On microscopical examination the viscera and central nervous system presented the following appearances.

Nissl Method.—Sections from the cerebral cortex, the mesencephalon, and spinal cord presented no evidence of any morbid change.

Busch Method.—Sections from the cortex, mesencephalon, medulla, various levels of the spinal cord, sciatic nerve, and muscles of the hind limb were examined and found to contain no degeneration.

Hæmatoxylin and Eosin.—Sections from the medulla and spinal cord showed no change in the nervous tissue, in the meninges, or in the vessels. The heart muscle, skeletal muscle, liver, and kidneys were apparently healthy.

Rat B.—Injected subdurally and intraperitoneally.

Day of Experiment.	Dose given.	Total Dose received.
1st day	·25 c.c. 2 per cent. sol.	·005 gram.
4th "	·25 " 4 "	·015 "
7th "	·25 " 4 "	·025 "
11th "	·25 " 4 "	·035 "
15th "	·25 " 4 "	·045 "
18th "	·25 " 4 "	·055 "
28th "	·25 " 2 "	·060 "
31st "	·25 " 2 "	·065 "

Day of Experiment.	Dose given.	Total Dose received.
35th day.	2·00 c.c. 2 (intraperitoneal)	·105 gram.
39th "	1·5 " 2 per cent. sol.	·135 "
43rd "	1·00 " 4 "	·175 "
47th "	1·00 " 4 "	·215 "
50th "	1·25 " 4 "	·265 "
53rd "	1·25 " 4 "	·315 "
56th "	1·25 " 4 "	·365 "
59th "	1·25 " 4 "	·415 "
64th "	1·00 " 10 "	·515 "
68th "	·15 " 10 " (subdural)	·530 "
71st "	1·25 " 4 "	·540 "
73rd "	·25 " 4 "	·550 "
77th "	·25 " 10 "	·575 "
80th "	·20 " 5 "	·585 "
97th "	—Rat killed.	

Clinical Symptoms.—8th day, diarrhoea persistent. 40th day, animal becoming lethargic and slow in movements.

After large dose on the 64th day, salivation and lachrymation marked; no convulsions.

After strong sub-dural dose on the 68th day, tetanic convulsions instantly supervened; salivation marked; half an hour later animal had recovered.

71st day: slight circus movements; stupor, but no convulsions.

77th day: slight circus movements in ten seconds; tetanic spasms of extreme severity supervened in one minute; violent spasms and convulsions lasted one hour, animal having to be restrained. If released it rushed blindly round room, and jumped wildly into the air. Recovery. No subsequent symptoms up to time of death.

Post-mortem.—No gross changes seen.

Nissl Method.—Sections from the cortex, mesencephalon, pons, medulla, and spinal cord were examined and found normal.

Weigert-Pal Method.—Sections from the cortex, pons, medulla, and cord showed no change in the medullated fibres.

Busch Method.—No degeneration was found in sections from the cortex, mesencephalon, and cord.

Hematoxylin and Eosin.—The heart, intestine, liver, and spleen were examined with negative results. The kidneys showed capillary engorgement and capillary hæmorrhages, with some cloudy swelling of the convoluted tubules.

In order to determine the approximate fatal dose for these animals, rat C was given .7 c.c. of a 10 per cent. solution of choline intraperitoneally. Salivation and lachrymation became very profuse, and the heart-beat intermittent. In two or three minutes slight convulsions supervened, but in ten minutes the animal had practically recovered.

The following day 1 c.c. of a 10 per cent. solution was given. The resulting symptoms were similar but more severe, the animal recovering in about an hour. Four days later the same dose was repeated. Tonic convulsions were produced, and respiration failed in five minutes, although the heart continued to beat for an hour. Post-mortem, no gross changes were detected.

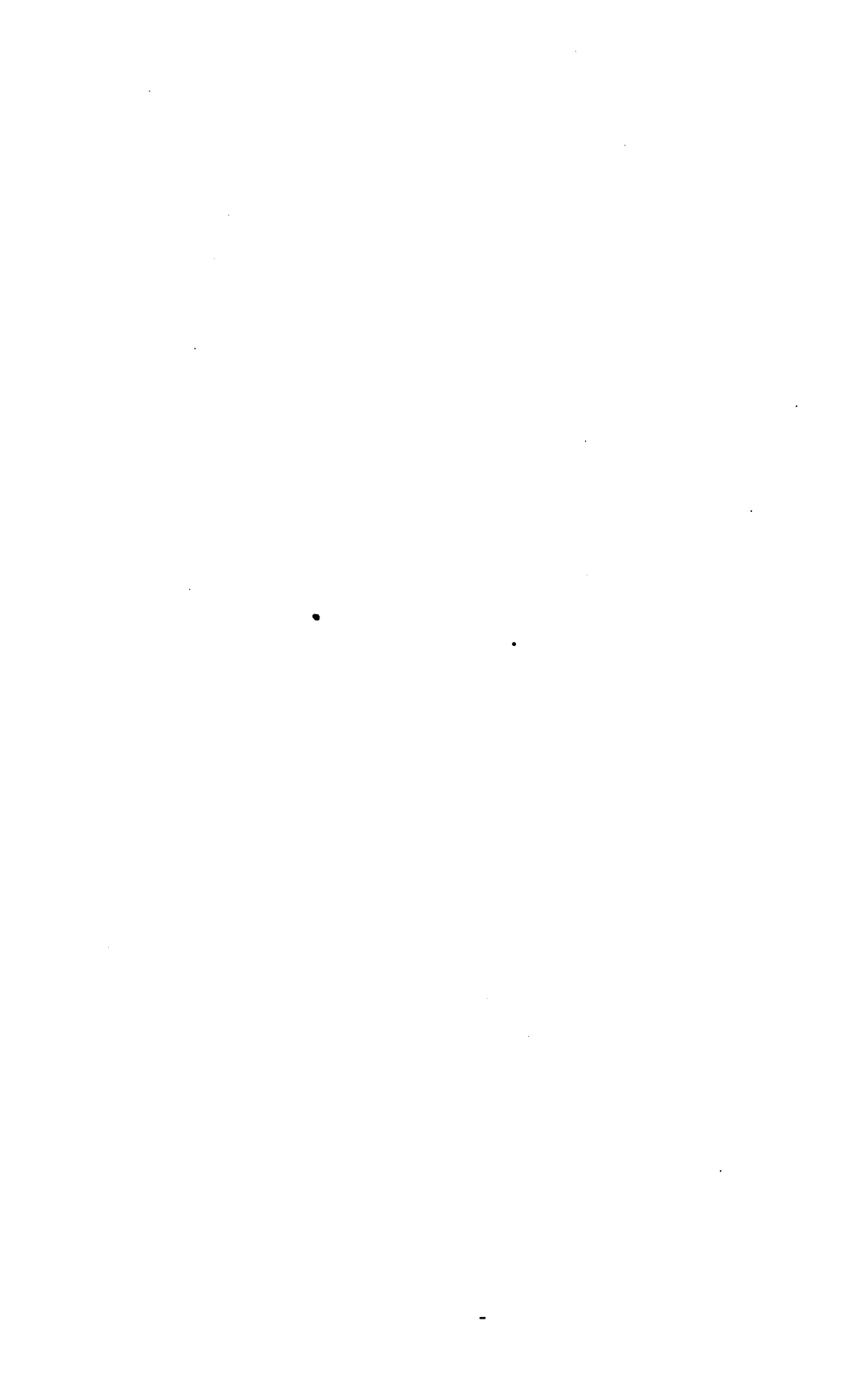
CONCLUSIONS.

1. The repeated introduction of moderate doses of choline into the circulating fluids of an animal produces neither convulsions nor paralytic phenomena.

2. The introduction of very large doses of the same substance produces convulsions, but the doses necessary are relatively greatly in excess of what can be produced in the human subject by the ordinary degenerations of the central nervous system.

3. It is improbable, therefore, that the convulsions of general paralysis or of epilepsy are directly or solely produced by the presence of choline in the blood or cerebro-spinal fluid.

4. The presence of considerable quantities of choline in the circulation does not produce morbid changes of importance in the central or peripheral nervous system or in the visceral organs of the body.



LIST

OF

GENTLEMEN EDUCATED AT GUY'S HOSPITAL

WHO HAVE PASSED THE

EXAMINATIONS OF THE SEVERAL UNIVERSITIES, OR OBTAINED OTHER DISTINCTIONS, DURING THE YEAR 1904.

University of Oxford.

Degree of Doctor of Medicine.

H. S. French.

Degree of Master in Surgery (M.Ch.)

P. N. Blake Odgers.

Second M.B. Examination.

Medicine, Surgery, Midwifery, Forensic Medicine and Public Health

R. A. Chisolm.		A. R. Wilson.		A. F. Hertz.
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Pathology.

R. A. Chisolm.		L. J. J. Orpen.
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First M.B. Examination.

O. G. F. Luhn.

University of Cambridge.

Degree of Master in Surgery (M.C.)

A. R. Brailey.

Final Examination for the Medical and Surgical Degrees

Part II.

S. Child. H. M. Clarke. J. Goss. E. C. Hughes.		T. C. Lucas. W. M. Mollison. F. W. Morton Palmer. O. V. Payne. E. W. Sheaf.		C. M. Stevenson. B. H. Stewart. G. A. Ticehurst. F. L. Woods.
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Part I.

F. D. Crew.		C. F. Fothergill.
L. G. Davies.		C. W. Greene.
E. C. Hughes.		

Second Examination for the Medical and Surgical Degrees.

H. J. B. Cane.		C. E. M. Jones.		B. K. Nutman.
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Diploma of Tropical Medicine and Hygiene.

Captain J. C. B. Statham, R.A.M.C.

Examination in Sanitary Science.

E. G. Allport.		M. Coplans.		R. D. Smedley.
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University of London.

Examination for the Degree of Doctor of Medicine.

A. Armer.		M. Coplans.		J. F. Northcott.
H. Barber.		T. Holmes.		G. S. Robertson.
M. Abdy Collins.		N. N. A. Houghton.		G. T. Wrench.
		G. E. Malcomson.		

Examination for the Degree of Master in Surgery.

W. H. Bowen.

Examination for the Degree of Bachelor of Surgery.

H. M. Goldstein.		D. L. Morgan.		E. C. Myott.
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Examination for the Degree of Bachelor of Medicine.

May.

First Division.

H. D. Smart.

Second Division.

H. H. Carter.		H. S. Jones.		E. C. Myott.
J. H. Clatworthy.		M. G. Louisson.		P. A. Peall.
P. W. Hamond.		H. C. C. Mann.		C. B. Penny.
C. E. Iredell.		B. Moiser.		G. W. Russell.

Examination for the M.B., B.S. Degrees.

October.

Obtained Honours.

* A. Leeming. | † F. Rogerson.

* *Distinguished in Midwifery and Diseases of Women.*

† *Distinguished in Surgery.*

Pass.

W. N. May. | J. McF. W. Pollard. | C. M. Wenyon.

Passed in Surgery, Midwifery, and Diseases of Women only.

E. Evans. | R. Felton.

General Intermediate Examination in Medicine.

Internal Students.

January.

G. F. E. Allison. | P. D. F. Magowan. | E. Wragg.
S. W. Daw. | R. J. Reynolds. | A. Zorab.

External Students.

A. Alcock. | G. B. F. Churchill.

July.

C. A. Basker. | H. J. Henderson. | E. L. R. Norton.
T. E. A. Carr. | J. E. Hodson. | H. J. Smith.
K. H. Digby. | C. A. L. Mayer. | G. F. Stebbing.
E. W. Giesen. | W. P. H. Munden.

Special Examination in Organic Chemistry only.

Internal Students.

January.

S. H. C. Air. | A. F. W. Denning. | H. E. Perkins.
L. T. Baker. | K. H. Digby. | M. D. Price.
M. E. Ball. | E. W. Giesen. | M. J. Rattray.
C. A. Basker. | H. J. Henderson. | J. T. Smalley.
S. S. Brook. | E. L. Mandel. | H. J. Smith.
T. E. A. Carr. | J. B. Martin. | G. F. Stebbing.
M. M. Cowasjee. | C. A. L. Mayer. | H. Stott.
L. Croft. | W. P. H. Munden. | St. J. A. M. Tolhurst.

External Students.

S. Chelliah.

July.

M. M. Adams. | A. L. Gardner. | R. A. Rankine.
H. B. Bastard. | K. H. Hole. | D. Reynolds.
H. B. Carter. | H. I. Janmahomed. | H. A. Sanford.
S. J. Darke. | W. Johnson. | T. Stausfield.
J. B. Dunning. | H. C. Lucey. | P. Seymour Price.
R. C. V. Edsall. | C. H. Marshall. | S. G. Tracy.
T. Evans. | B. McDermott. | V. Townrow.
H. E. H. Mitchell.

External Student.

G. B. Harland.

Preliminary Scientific Examination for Internal Students.

January.

Chemistry and Biology.

* A. N. Leeming.

Biology and Experimental Physics.

J. Pryce Davies.

Biology only.

P. Hirschbein.

| * W. S. Kidd.

These Candidates have already passed in Experimental Physics.

External Student.

Biology.

* H. I. Janmahomed.

* *This Candidate has already passed part of the Examination.*

July.

Entire Examination.

C. A. Wood.

Chemistry and Biology.

A. A. Greenwood.

Experimental Physics and Biology.

C. H. Crump.

| J. L. Johnson.

| J. R. Perdrau.

E. L. Elliott.

| T. L. Jones.

| A. F. Sabin.

G. F. Haycraft.

| G. H. Peall.

| C. Witts.

Chemistry only.

* W. S. Kidd.

| * W. E. Williams.

Experimental Physics only.

A. Archer.

Biology only.

A. L. Fitzmaurice.

| D. A. Mitchell.

| * R. A. Rankine.

* *Denotes completion of Examination.*

External Student.

Chemistry and Experimental Physics.

W. L. Hibbert.

University of Durham.

Examination for the Degree of Doctor in Medicine.

M. C. Wetherell.

*Examination for the Degree of Doctor in Medicine for Practitioners
of Fifteen Years' Standing.*

F. K. Holman.
A. Hooper.

T. S. Jones.
H. E. Rowell.

*Final Examination for the Degrees of Bachelor of Medicine
and Bachelor of Surgery.*

O. B. Travers.

Third Examination.

A. A. Smith.

First Examination.

Chemistry and Physics.

H. C. W. Allott.

L. W. Evans.

A. C. Greene.

Anatomy and Biology.

L. K. Edmeades.
E. P. L. Hughes.

S. L. Randolph.
J. F. Young.

Royal College of Physicians of London.

Examination for the Diploma of Membership.

D. Forsyth.

Final Examination for the License.

January.

P. P. Cole.
J. B. Copland.
C. M. L. Cowper.
H. B. German.

F. P. Hughes.
M. G. Louisson.
R. Moyle.
C. M. Murray.

J. F. Rey.
G. A. Ticehurst.
A. H. Turner.
E. L. Ward.

April.

H. O. M. Beadnell.
J. C. O. Bradbury.
J. Bromley.

H. F. Hatfield.
B. Moiser.
C. S. Morris.

G. Nunn.
F. H. Parker.
E. W. Routley.

H. M. M. Woodward.

July.

F. Alcock.	E. C. Hughes.	W. M. Mollison.
F. Barnes.	S. D. Jacobson.	M. J. Mottram.
C. E. Bartlett.	H. H. Jenkins.	E. C. Myott.
J. E. L. Bates.	M. Maher.	J. H. F. Roberts.
F. G. Goble.	W. N. May.	G. C. F. Robinson.

October.

A. R. Beaumont.	R. Felton.	W. T. P. Meade-King.
A. M. Benett.	F. C. R. M. Knight.	J. McF. W. Pollard.
G. Carlisle.	A. E. F. Kynaston.	G. H. Rees.
J. Cook.	A. Leeming.	F. Rogerson.
C. H. Denyer.	A. J. Littlejohns.	C. M. Stevenson.

Royal College of Surgeons of England.

Final Examination for the Fellowship.

K. Black.	H. Davies-Colley.	N. I. Spriggs.
A. R. Brailey.	F. H. Parker.	

First Examination for the Fellowship.

S. W. Daw.	E. M. Pileher.
S. E. Denyer.	E. Wragg.

Final Examination for the Membership.

January.

P. P. Cole.	F. P. Hughes.	J. F. Rey.
J. B. Copland.	M. G. Louissou.	G. A. Ticehurst.
C. M. L. Cowper.	R. Moyle.	A. H. Turner.
H. B. German.	C. M. Murray.	E. L. Ward.

April.

H. O. M. Beadnell.	H. F. Hatfield.	G. Nunn.
J. C. O. Bradbury.	B. Moiser.	F. H. Parker.
J. Bromley.	C. S. Morris.	E. W. Routley.
	H. M. M. Woodward.	

July.

F. Alcock.	E. C. Hughes.	W. M. Mollison.
F. Barnes.	S. D. Jacobson.	M. J. Mottram.
C. E. Bartlett.	H. H. Jenkins.	E. C. Myott.
J. E. L. Bates.	M. Maher.	J. H. F. Roberts.
F. G. Goble.	W. N. May.	G. C. F. Robinson.

October.

A. R. Beaumont.	R. Felton.	W. T. P. Meade-Kin
A. M. Bennett.	F. O. R. M. Knight.	J. MoF. W. Pollard.
G. Carlisle.	A. E. F. Kynaston.	G. H. Rees.
J. Cook.	A. Leeming.	F. Rogerson.
C. H. Denyer.	A. J. Littlejohns.	S. M. Stevenson.

Examination for the Diploma in Public Health.

S. C. Clapham.	M. J. Rees.	J. C. B. Statham.
J. W. Gromitt.	J. R. Steinhæuser.	

Society of Apothecaries of London.

J. Bromley.

Royal College of Surgeons of Edinburgh.

Examination for the Fellowship.

A. D. E. Kennard.		W. S. Richardson.
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Naval Medical Service.

F. R. Featherstone.		G. Moir.
H. B. German.		G. Nunn.

Royal Army Medical Corps.

R. G. Anderson.	S. C. Bowle.	G. S. C. Hayes.
H. O. M. Beadnell.	A. W. Gater.	T. O. Lucas.
	H. C. Winckworth.	

Indian Medical Service.

H. Watts,

MEDALLISTS AND PRIZEMEN,

JULY, 1905.

Open Scholarships in Arts.

Geoffrey Dunderdale, Clifton College, £100.

William Henry Catto, Royal College, Mauritius, £50.

Marc Antoine Emile Duvivier, Royal College, Mauritius, Certificate.

Open Scholarships in Science.

Charles Albert Wood, Guy's Hospital, £150.

Guy Fleetwood Haycraft, Guy's Hospital, £60.

Hugh Braund Kent, The Northern Polytechnic, Certificate.

Scholarship for University Students.

Patrick Playfair Laidlaw, B.A., St. John's College, Cambridge, £50.

Open Scholarships in Dental Mechanics.

October, 1904, John Richard Doren Ditch, £20.

May, 1905, William Francis Boxall, £20.

Junior Proficiency Prizes.

Harry Archibald Sanford, £20.

Arthur Norman Leeming, £15.

Vincent Townrow, £10.

William Johnson, Certificate.

The Michael Harris Prize for Anatomy.

Gilbert Francis Syms, £10.

The Wooldridge Memorial Prize for Physiology.

Harry Archibald Sanford, £10.

Leonard Tilsley Baker, Certificate.

The Hilton Prize for Dissections.

Edward Leslie Martyn Lobb, £5.

The Arthur Durham Prizes for Dissection.

First Year's Students.

Hugh Braund Kent, £5.

George Dunlop Martin, Certificate.

Senior Students.

Edward Leslie Martyn Lobb, £15.

Harry Archibald Sanford, Certificate.

Dental Prizes.

First Year's Students.

Harold Todd Reeve, £10.

Frank Maurice Holborn, Certificate.

Horace Edmund Marsh, Certificate.

Second Year's Students (1904).

Arthur Alan Forty	}	Equal
James William Mawer		£7 10s. each.

Practical Dentistry Prize.

Fritz Julian Messer, £10.

The Golding-Bird Gold Medal and Scholarship in Bacteriology.

Edwin Walter Routley, £20.

THE PHYSICAL SOCIETY.**Honorary President.**—Sir SAMUEL WILKS, Bart., M.D., LL.D., F.R.S.**Secretaries.**—H. S. French, M.A., M.D.; H. T. Hicks.**Presidents.**

E. H. B. Milsom, M.B., B.S., H. F. B. Walker, M.B., F. W. M. Palmer, B.A., G. A. Ticehurst, B.A., W. M. Mollison, B.A., A. R. Brailey, B.A., M.B., B.C., H. C. Cameron, M.A., J. S. Cooper, M.A., M.B., B.C., A. F. Hertz, B.A., G. Russell, M.B., N. I. Spriggs, M.B., B.S., K. H. Digby, G. H. K. Macalister, B.A., G. C. F. Robinson.

Session 1904-1905.—The Society's Prize of £10 was obtained by Mr. R. G. Anderson, for his paper "Thrombosis and Embolism as Complications of Surgical Operations."

**CLINICAL APPOINTMENTS HELD DURING THE
YEAR 1904.**

HOUSE PHYSICIANS.

G. E. Malcomson.
B. H. Wedd.
W. F. Box.

H. F. Bell Walker.
B. Glendining.
H. C. C. Mann.

J. Goss.
E. H. B. Milsom.

HOUSE SURGEONS.

K. Black.
A. R. Brailey.
A. M. Webber.

N. I. Spriggs.
L. S. H. Glanville.
R. G. Anderson.

C. D. Pye-Smith.
R. A. Greeves.

ASSISTANT HOUSE PHYSICIANS.

H. C. C. Mann.
W. F. Box.

E. H. B. Milsom.
B. H. Wedd.

J. Goss.
H. F. Bell Walker.

ASSISTANT HOUSE SURGEONS.

F. H. Wallace.
W. F. Box.
E. H. B. Milsom.
H. F. Bell Walker.
G. A. Ticehurst.
R. A. Greeves.
J. S. Cooper.

R. G. Anderson.
J. Goss.
P. C. Bent.
A. M. Webber.
E. L. Ward.
M. G. Louisson.
J. H. Clatworthy.

P. A. Peall.
N. I. Spriggs.
P. P. Cole.
F. P. Hughes.
H. Watts.
B. H. Stewart.
C. E. Iredell.

OUT-PATIENTS' OFFICERS.

A. F. Hertz.
M. G. Louisson.

W. M. Mollison.
G. A. Ticehurst.

OBSTETRIC RESIDENTS.

F. D. S. Jackson.
P. A. Peall.
E. L. Ward.

C. H. Reinhold.
E. W. Strange.
P. C. V. Bent.

E. G. Goldie.
F. H. Wallace.
H. Watts.

CLINICAL ASSISTANTS.

E. H. B. Milsom.
C. D. Pye-Smith.
J. S. Cooper.
E. P. Hughes.
C. E. Iredell.
W. M. Mollison.
F. Alcock.
M. J. Mottram.

H. F. Bell Walker.
P. P. Cole.
G. A. Ticehurst.
R. A. Greeves.
A. F. Hertz.
O. V. Payne.
J. M. Barrionuevo.
G. C. F. Robinson.

A. M. Webber.
M. Coplans.
M. G. Louisson.
E. L. Ward.
B. Moiser.
B. H. Stewart.
H. H. Carter.
H. M. M. Woodward.

CLINICAL ASSISTANTS IN THE MEDICAL WARDS.

G. H. Cheyney.
A. F. Hertz.
G. C. F. Robinson.
R. W. Allen.
R. O. Williams.

O. V. Payne.
J. M. Barrionuevo.
F. W. M. Palmer.
W. N. May.
H. D. Wyatt.
A. D. Crofts.

A. R. Beaumont.
A. V. Maybury.
F. Rogerson.
C. M. Stevenson.
A. R. Wilson.

CLINICAL ASSISTANTS IN THE SURGICAL WARDS.

T. Turner.
R. O. Williams.
M. Maher.
J. E. Collins.

M. Mottram.
H. P. Costobadie.
M. B. Taylor.
R. W. Allen.

W. N. May.
W. S. Orton.
A. M. Benett.

SURGEONS' DRESSERS.

H. G. Gibson.
C. C. De Villiers.
A. S. M. Palmer.
T. H. Barton.
C. M. Ockwell.
J. S. Bookless.
W. Welchman.
E. C. Lowe.
W. P. Purdom.
I. R. Cook.
R. S. Harper.
F. A. Sharpe.
G. W. Nicholson.
F. W. M. Palmer.
C. W. R. Preston.
H. F. Wight.
T. C. Pocock.
V. A. Costobadie.
E. H. Adams.
F. T. H. Wood.
G. Hamilton.
R. P. Lewis.
N. H. Oliver.
H. V. Mitchell.
M. De T. Robinson.

R. E. French.
P. S. Mills.
E. Alban.
S. Reader.
W. H. Trethowan.
A. G. Jones.
T. F. Wilson.
C. W. Ponder.
E. M. Harrison.
R. J. Bentley.
T. R. Harvey.
M. Leckie.
R. M. Wingent.
H. A. Watney.
E. H. Adams.
J. H. Mayston.
J. A. C. Greene.
E. F. Milton.
A. H. Miller.
H. S. Knight.
A. H. Clough.
H. M. Langdale.
A. Morris.
H. C. Cameron.
R. A. Chisolm.

R. W. Allen.
P. C. Litchfield.
A. W. Eyles.
F. Vandermin.
A. W. Berry.
A. S. B. Bankart.
G. Wachter.
W. H. S. Burney.
W. H. Robinson.
H. G. Gibson.
E. E. Rendle.
G. H. Morris.
E. B. Smith.
C. F. Fothergill.
B. B. Metcalfe.
L. H. Burner.
T. Norman.
J. E. Scales.
G. H. K. Macalister.
W. C. Dickey.
G. F. Greening.
R. D. Barron.
A. D. Croft.
A. B. O'Brien.
F. D. Crew.

DENTAL SURGEONS' DRESSERS.

G. A. Ticehurst.	E. L. Ward.	A. M. Webber.
F. Rogerson.	W. T. Meade-King.	H. V. Mitchell.
G. H. Rees.	A. M. Bennett.	A. R. Wilson.
R. P. Lewis.	R. P. Langdale.	

ASSISTANT SURGEONS' DRESSERS.

R. J. Bentley.	T. C. Pocock.	H. A. Watney.
B. B. Metcalfe.	G. Hamilton.	E. H. Adams.
E. B. Smith.	F. T. H. Wood.	G. W. Nicholson.
W. P. Purdom.	M. Leckie.	H. S. Knight.
F. A. Sharpe.	R. S. Harper.	E. F. Milton.
T. Norman.	H. F. Wight.	E. E. Rendle.
C. M. Ockwell.	L. H. Burner.	W. H. S. Burney.
T. F. Wilson.	P. S. Mills.	S. Reader.
G. N. Bartlett.	E. M. Harrison.	E. C. Lowe.
H. T. Vandermin.	A. S. M. Palmer.	C. F. Fothergill.
H. G. Gibson.	G. Wachter.	A. G. Jones.
P. C. Litchfield.	J. H. Mayston.	T. R. Harvey.
R. M. Wingent.	I. R. Cook.	E. Alban.
A. W. Berry.	C. C. De Villiers.	G. H. Morris.
E. L. R. Norton.	A. W. Eyles.	P. D. Magowan.
H. Moyle.	J. G. Phillips.	C. Shepherd.
G. Cockcroft.	W. H. Trethowan.	A. Walker.
F. A. Barker.	T. H. Barton.	C. W. Greene.
J. S. Bookless.	A. S. B. Bankart.	R. Davies-Colley.
G. Goodhart.	C. W. Ponder.	W. H. Robinson.
I. Valerio.	H. J. Clarke.	R. Willan.
J. A. Wiehe.	H. E. H. Tracy.	J. L. Rankine.
W. R. Greening.	J. S. Farnfield.	C. F. L. Leipoldt.
W. H. Miller.	E. Morgan.	H. C. Malleon.
A. Alcock.	T. B. Layton.	H. A. Pallant.
A. Zorab.	J. E. Hodson.	G. R. Phillips.
E. H. Paterson.	E. Paterson-Clavier.	H. W. B. Walling.

CLINICAL ASSISTANTS IN MEDICAL OUT-PATIENTS.

D. H. Richards.	G. C. F. Robinson.	G. Russell.
J. M. Barrionuevo.	L. Myer.	A. M. Bennett.
H. Carter.	R. M. Rendall.	

OPHTHALMIC DRESSERS.

M. Maher.	F. B. Lowe.	A. M. Bennett.
A. V. Maybury.	R. Franklin.	E. Lloyd.
R. Edridge.	W. Reeve.	A. R. Beaumont.
G. Russell.	E. C. Myott.	D. Isaacs.
R. M. Rendall.	H. M. Langdale.	E. M. Wenyon.
A. E. F. Kynaston.	R. Felton.	R. O. Williams.
P. P. Cole.	A. D. Crofts.	F. W. M. Palmer.
A. Leeming.	O. V. Payne.	H. M. Clarke.
R. E. French.	E. C. Hughes.	F. Rogerson.
B. H. Wedd.	B. W. Lacey.	T. Turner.
M. de L. Robinson.		

DRESSERS IN THE THROAT DEPARTMENT.

H. M. Goldstein.	F. Barnes.	J. H. Clatworthy.
J. S. Cooper.	A. R. Wilson.	R. A. Greeves.
G. Carlisle.	H. H. Jenkins.	J. McF. W. Pollard.
W. M. Mollison.	F. W. M. Palmer.	C. E. Iredell.
H. D. Wyatt.	H. M. Clarke.	E. W. Sheaf.
F. Alcock.	H. C. C. Mann.	A. R. Brailey.
A. V. Maybury.	S. M. Wells.	E. C. Hughes.
R. Felton.		

CLERKS IN THE THROAT DEPARTMENT.

C. Myer.	M. G. Louisson.	I. R. Cook.
F. B. Lowe.		

MEDICAL WARD CLERKS.

A. G. Jones.	L. H. Burner.	A. Shepperd.
G. H. Morris.	H. G. Gibson.	J. H. Mayston.
A. S. M. Palmer.	E. L. R. Norton.	C. F. Fothergill.
G. N. Bartlett.	T. H. Barton.	A. W. Eyles.
E. M. Harrison.	E. C. Lowe.	W. H. S. Burney.
T. F. Wilson.	E. Alban.	C. C. De Villiers.
J. S. Bookless.	H. F. Vandermin.	A. W. Berry.
G. Wachter.	G. G. Timpson.	W. Welchman.
P. S. Mills.	E. Morgan.	W. H. Trethowan.
S. Reader.	C. W. Ponder.	C. M. Ockwell.
W. H. Robinson.	A. S. B. Bankart.	A. Walker.
G. Cockeroff.	P. D. F. Magowan.	I. Valerio.
H. C. Malleson.	R. Willan.	R. Davies-Colley.
G. W. Goodhart.	F. A. Barke	C. W. Greene.
H. J. Clarke.	J. A. Wiehe.	J. G. Phillips.
H. W. B. Walling.	E. H. Paterson.	J. E. Hodson.
T. B. Layton.	P. F. McEvedy.	W. H. Miller.
H. A. Pallant.	G. R. Phillips.	H. E. H. Tracy.
A. Zorab.	J. S. Farnfield.	C. F. L. Leipoldt.
E. P. Minett.	J. L. Rankine.	A. Alcock.
S. K. Poole.	J. T. Smalley.	G. F. E. Allison.
S. W. Daw.	R. F. Rivers.	E. Wragg.
. Davidson.	M. M. Earle.	C. E. M. Jones.
. F. Luhn.	B. K. Nathan.	H. H. Moyle.

ASSISTANT PHYSICIANS' CLERKS.

E. Alban.	A. W. Berry.	C. C. De Villiers.
G. Wachter.	G. N. Bartlett.	E. M. Harrison.
H. V. Vandermin.	E. C. Lowe.	T. F. Wilson.
S. Reader.	P. S. Mills.	I. R. Cook.
T. R. Harvey.	R. M. Wingent.	E. White.
P. C. Litchfield.	A. S. M. Palmer.	L. H. Burner.
A. G. Jones.	C. F. Fothergill.	

CLERKS IN THE SKIN DEPARTMENT.

C. W. Greene.	S. M. Wells.	E. M. Harrison.
E. C. Lowe.	A. S. B. Bankart.	H. M. Clarke.
J. H. Clatworthy.	R. A. Greeves.	

AURAL SURGEONS' DRESSERS.

W. N. May.	G. F. Hardy.	J. W. Dadd.
B. W. Lacey.	W. M. Mollison.	E. C. Myott.
F. Rogerson.	J. M. Barrionuevo.	H. Carter.
A. R. Brailley.	E. W. Sheaf.	F. Barnes.

ASSISTANT SURGEONS' CLERKS.

W. R. Greening.	N. Flower.	W. H. Miller.
J. B. Ball.	J. L. Rankine.	G. N. Bartlett.
T. H. Barton.	I. R. Cook.	I. R. Florence.
C. H. Paterson.	A. T. Rivers.	G. F. Hardy.
J. W. Featherstone.	C. L. Leipoldt.	F. Morris.
	F. H. Fuller.	

POST-MORTEM CLERKS.

D. Isaacs.	G. Hamilton.	A. S. Littlejohns.
J. H. Clatworthy.	A. R. Beaumont.	A. M. Roome.
G. H. Rees.	J. D. Thomas.	F. Alcock.
S. M. Wells.	C. J. S. Dismorr.	C. M. Stevenson.
F. D. Crew.	E. C. Hughes.	A. Leeming.
C. M. Wenyon.	R. Felton.	R. E. French.
E. Evans.	M. De L. Robinson.	B. W. Lacey.
T. E. Pocock.	R. W. Allen.	F. B. Lowe.
R. O. Williams.	F. Rogerson.	F. M. Longson.
L. J. J. Orpen.	H. S. Knight.	F. H. T. Wood.
A. B. O'Brien.	T. Turner.	I. R. Cook.
	L. G. Davies.	

OBSTETRIC DRESSERS.

H. S. Jones.	G. F. Greening.	E. Lloyd.
F. W. M. Palmer.	G. H. Rees.	E. C. Myott.
F. Rogerson.	R. D. Bridger.	F. M. Longson.
R. O. Williams.	J. M. Barrionuevo.	R. W. Allen.
R. Felton.	T. Turner.	W. N. May.
F. Alcock.	D. Isaacs.	E. W. Sheaf.
H. M. Clarke.	A. Leeming.	V. A. P. Costobadie.
R. F. Lewis.	S. M. Wells.	E. C. Hughes.
E. F. Milton.	C. M. Wenyon.	J. E. Scales.
M. De L. Robinson.	A. H. Clough.	T. Norman.
F. A. Sharpe.	G. Hamilton.	H. A. Watney.
	F. D. Crew.	

EXTERN OBSTETRIC ATTENDANTS.

N. H. Oliver.
H. M. Langdale.
F. M. Longson.
C. M. Stevenson.
F. Alcock.
L. G. Davies.
P. A. S. Dyson.
A. Leeming.
R. P. Lewis.
A. B. O'Brien.
F. Burton Brown.
T. Turner.
V. A. P. Costobadie.
F. D. Crew.
J. A. C. Greene.
F. T. H. Wood.
S. Reader.
A. W. Eyles.
L. H. Burner.
R. S. Harper.
W. P. Purdom.
E. H. Adams.

A. Morris.
G. Russell.
H. D. Wyatt.
S. M. Wells.
E. C. Hughes.
L. Doudney.
H. B. Cocker.
E. White.
W. C. Dickey.
A. D. Crofts.
R. O. Williams.
R. Edridge.
H. C. Cameon.
G. H. K. Macalister.
C. W. R. Preston.
A. H. Miller.
A. Walker.
G. W. Nicholson.
E. B. Smith.
B. B. Metcalfe.
M. Leckie.
R. W. Allen.

R. E. French.
L. J. J. Orpen.
H. M. Clarke.
E. W. Sheaf.
R. Felton.
R. M. Wenyon.
H. P. Costobadie.
R. D. Barron.
F. A. Sharpe.
I. R. Cook.
M. De L. Robinson.
R. A. Chisolm.
G. Hamilton.
H. S. Knight.
G. F. Greening.
T. Norman.
H. P. Wight.
W. Reeve.
H. V. Mitchell.
T. R. Harvey.

CLERKS TO ANÆSTHETISTS.

A. B. O'Brien.
A. D. Crofts.
A. E. Kynaston.
I. R. Cook.
G. H. Cheyney.
J. D. Thomas.
A. F. Harts.
C. M. Stevenson.
H. M. Clarke.
S. M. Wells.
E. W. Sheaf.
R. A. Chisolm.
F. Rogerson.
F. B. Lowe.
C. M. Wenyon.
W. C. McN. Dickey.
G. F. Hardy.
H. M. Langdale.
F. A. Sharpe.
J. E. Scales.
A. Morris.
A. H. Miller.
C. M. Ockwell.
E. Lloyd.
A. H. Clough.
G. H. Morris.
R. J. Bentley.
J. O. Musson.

V. A. Costobadie.
J. M. Barrionuevo.
A. S. Littlejohns.
M. Maher.
B. Moiser.
M. Mottram.
F. M. Longson.
C. J. S. Dismorr.
E. C. Hughes.
G. C. F. Robinson.
H. D. Wyatt.
E. N. Jupp.
G. F. Greening.
P. A. S. Dyson.
R. D. Barron.
M. De L. Robinson.
R. W. Allen.
R. P. Lewis.
F. T. H. Wood.
H. V. Mitchell.
T. Turner.
R. E. French.
H. N. Oliver.
J. E. L. Bates.
L. J. J. Orpen.
E. B. Smith.
J. A. C. Greene.
H. A. Watney.

A. R. Beaumont.
J. M. Pollard.
J. H. Clatworthy.
W. S. Orton.
C. M. Murray.
P. F. Minett.
C. P. Harvey.
J. E. Collins.
F. Alcock.
R. O. Williams.
A. Leeming.
R. Felton.
G. Russell.
A. B. Cocker.
L. Myer.
L. G. Davies.
A. M. Benett.
F. D. Crew.
H. S. Knight.
F. W. M. Palmer.
G. Carlisle.
H. P. Wight.
H. C. Cameron.
L. Doudney.
C. W. R. Preston.
W. Reeve.

DENTAL SCHOOL

APPOINTMENTS HELD DURING THE YEAR 1904.

HOUSE SURGEONS.

A. E. D. Prideaux.	J. H. Williams.	E. L. Pilbeam.
B. H. Martin (3 months).	C. W. Randall (3 m'ths).	

ASSISTANT HOUSE SURGEONS.

E. L. Pilbeam.	J. H. Williams.	P. Hickman.
J. W. Mawer.	F. A. Husbands.	F. S. Vine.
J. B. Ball.	S. A. Piper.	

DEMONSTRATORS IN THE CONSERVATION ROOM.

J. Bollard.	W. Elwood.	F. S. Vine.
F. A. Husbands.	S. A. Piper.	H. Snell.
J. B. Ball.	A. Alan Forty.	G. G. Timpson.
A. W. Parrott.	R. G. Yates.	D. G. Wearing.

DRESSERS IN THE GAS ROOM.

P. H. Hickman.	J. A. Oates.	J. W. Mawer.
H. G. Pearce.	A. Hammond Smith.	S. A. Piper.
F. J. Goodman.	H. J. Snowden.	V. S. Houchin.
W. A. Helyer.	W. E. Cook.	R. M. Pearson.
F. A. Husband.	F. L. Aubrey.	S. D. Marshall.
A. Alan Forty.	H. A. Pallant.	H. E. H. Tracy.
A. Angell.	E. L. Pemberton.	D. G. Wearing.
R. S. Yates.	R. G. H. Warner.	H. Snell.
J. S. Vogwell.	W. J. Timberlake.	G. E. Rice.
A. R. Durant.	J. A. Bowes.	J. B. Ball.
W. J. Wormald.	H. M. Peacock.	A. S. Thomas.
J. Bollard.	F. A. Beckley.	A. W. Parrott.
W. J. P. Dicks.	E. S. Pierrepont.	T. Scott-Foster.
F. J. Cutler.	P. V. G. Pedrick.	T. L. Smith.
M. S. Philson.	H. J. Russell.	A. T. Dean.
F. J. Messer.	R. P. Fenn.	A. E. Webb.

DRESSERS IN THE EXTRACTION ROOM.

R. G. H. Warner.	A. W. Parrott.	F. J. Gillett.
T. Scott-Foster.	N. P. Rodgers.	J. A. Bowes.
O. B. Townshend.	H. J. Russell.	A. S. Thomas.
H. Snell.	R. P. Fenn.	E. S. Pierrepont.
F. J. Cutler.	W. J. P. Dicks.	R. J. Messent.
C. R. Rudolf.	A. E. Webb.	E. D. R. Jacob.
W. E. Freeman.	W. H. Plowman.	W. T. Dean.
W. T. Dicks.	H. J. Weighell.	A. R. Durant.
F. J. Messer.	O. J. Roots.	B. B. Samuel.
J. McBride.	C. Weller.	M. S. Philson.
H. E. Marsh.	C. M. Craig.	B. L. Weaver.
S. G. Elliott.	T. R. B. Ellis.	R. B. Gill.
R. A. Glindon.	G. Packham.	H. V. Sharp.
C. E. Lloyd.	H. L. Power.	H. G. Clark.
O. G. Iliffe.	C. G. G. Lewis.	F. M. Holborn.
H. Simms.	C. C. Freer.	H. G. Dumayne.
G. Warren.	E. L. Brown.	F. H. Crouch.
H. T. Reeve.		

DRESSERS IN THE CONSERVATION ROOM.

J. Bollard.	R. Beadnell-Gill.	F. H. Crouch.
P. E. Luce.	F. J. Goodman.	V. S. Houchin.
J. F. Ryder.	J. McL. Nibbs.	J. A. Oates.
A. B. Cocker.	H. J. Snowden.	G. E. Wood.
T. Scott-Foster.	W. E. Cook.	F. A. Husbands.
G. E. Rice.	J. W. Mawer.	H. G. Pearce.
H. M. Peacock.	R. G. Yates.	A. W. Parrott.
D. G. Wearing.	A. Hammond-Smith.	F. S. Vine.
A. R. Durant.	A. Harris.	F. W. Bartle.
S. D. Marshallsay.	W. Elwood.	P. H. Hickman.
W. J. C. Timberlake.	R. J. Messent.	C. L. Pemberton.
H. A. Pallant.	J. S. Vogwell.	W. J. Wormald.
H. Poyton.	W. R. Penford.	E. L. Pilbeam.
H. E. Warren-Williams.	N. P. Rodgers.	H. E. H. Tracy.
F. B. Ball.	J. H. Williams.	H. E. Alexander.
T. L. Smith.	F. A. Beckley.	W. A. Helyar.
R. G. H. Warner.	H. Snell.	A. S. Thomas.
H. J. Russell.	F. S. Aubrey.	W. C. McN. Dickey.
R. M. Pearson.	F. J. Gillett.	L. B. Moore.
F. J. Cutler.	C. Weller.	A. Angell.
E. N. Plummer.	F. H. Fuller.	A. Alan Forty.
W. L. Dean.	T. R. B. Ellis.	E. S. Pierrepont.
S. A. Piper.	W. J. P. Dicks.	C. M. Craig.
J. A. Bowes.	J. S. Vogwell.	F. H. Fuller.
J. Bollard.	H. E. Alexander.	J. A. Bowes.
J. McBride.	H. J. Weighell.	O. G. Iliffe.
A. S. Thomas.	N. P. Rodgers.	W. H. Plowman.
B. B. Samuel.	W. W. Cook.	E. D. R. Jacob.
W. E. Freeman.	F. J. Messer.	O. J. Roots.
R. C. B. Shaw	C. Weller.	P. V. G. Pedrick.

PROBATIONARY DRESSERS.

W. J. R. Dicks.	R. C. B. Shaw.	C. Weller.
R. Beadnell-Gill.	C. R. Rudolf.	C. M. Craig.
E. D. R. Jacob.	J. McBride.	E. S. Pierrepont.
O. J. Roots.	W. J. Weighell.	H. J. Weighell.
J. A. Bowes.	W. T. Dean.	R. P. Fenn.
W. E. Freeman.	P. J. Messer.	B. B. Samuel.
W. H. Plowman.	A. E. Webb.	E. L. Brown.
S. G. Elliott.	C. C. Freer.	G. Packham.
H. Simms.	B. L. Weaver.	H. G. Dumayne.
G. G. Lewis.	H. T. Reeve.	H. V. Sharp.
H. G. Clark.	F. M. Holborn.	C. E. Lloyd.
H. E. Marsh.	H. L. Power.	G. Warren.

JUNIOR AND CASUALTY DRESSERS.

W. E. Cook.	C. L. Pemberton.	D. G. Wearing.
W. A. Helyar.	R. M. Pearson.	W. J. C. Timberlake.
H. Snell.	R. G. Yates.	J. S. Vogwell.
F. J. Cutler.	A. R. Durant.	A. W. Parrott.
R. G. H. Warner.	G. E. Rice.	J. A. Bowes.
H. J. Russell.	T. Scott-Foster.	H. E. Alexander.
T. L. Smith.	A. S. Thomas.	F. J. Messer.
W. T. Dean.	J. McBride.	W. J. P. Dicks.
E. S. Pierrepont.	C. M. Craig.	R. P. Fenn.
A. E. Webb.	C. Weller.	M. S. Philson.
F. H. Crouch.	W. E. Freeman.	B. L. Weaver.
O. J. Roots.	F. J. Gillett.	W. H. Plowman.
H. J. Weighell.	E. D. R. Jacob.	B. B. Samuel.

LIST

OF

GENTLEMEN EDUCATED AT GUY'S HOSPITAL

WHO HAVE PASSED THE

EXAMINATIONS OF THE SEVERAL UNIVERSITIES, OR OBTAINED OTHER DISTINCTIONS, DURING THE YEAR 1905.

University of Oxford.

Degree of Doctor of Medicine.

O. W. Richards.

Degree of Master in Surgery (M.Ch.).

O. W. Richards.

Second M.B. Examination.

Pathology.

O. G. F. Luhn, C. J. Pinching.

Medicine, Surgery, Midwifery, Forensic Medicine, and Hygiene.

L. J. J. Orpen.

C. J. Pinching.

University of Cambridge.

Third Examination for Medical and Surgical Degrees.

Part II.

H. O. Cameron.
F. D. Crew.
L. G. Davies.

R. E. French.
E. Lloyd.
G. H. K. Macalister.

A. H. Miller.
G. W. de P. Nicholson.

Part I.

A. S. B. Bankart.
R. Davies-Colley.
A. Densham.

G. W. Dryland.
G. W. Goodhart.
E. Lloyd.
A. Walker.

G. W. de P. Nicholson.
A. S. Morton Palmer.
E. R. Stone.

Second Examination for Medical and Surgical Degrees.

W. E. Wallis.		C. S. E. Wright.
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Examination in Sanitary Science.

R. Denman.		E. W. Routley.
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University of London.

Examination for the Degree of Doctor of Medicine.

Branch I.—Medicine.

J. A. Butler.		A. H. Gerrard (Gold Medal).
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Branch IV.—Midwifery and Diseases of Women.

E. Collins.		N. Ivens Spriggs.
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Branch V.—State Medicine.

Examination for the Degree of Master in Surgery.

T. Holmes (Gold Medal).		A. M. Webber.
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Examination for the Degree of Bachelor of Surgery.

Obtained Honours.

H. C. C. Mann.		H. D. Smart.
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Pass.

L. S. H. Glanville.		M. G. Louisson.		C. D. Pye-Smith.
		F. L. Thomas.		

Examination for the M.B., B.S. Degrees.

May.

Obtained Honours.

R. O. Williams (Distinguished in Medicine, and in Midwifery, Diseases of Women).		
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Pass.

E. Evans.		F. M. Longson.		M. de L. Robinson.
R. Felton.		R. H. Rees.		F. T. H. Wood.

Supplementary Pass List.

Group I.—Medicine, Pathology, and Forensic Medicine.

P. C. P. Ingram.

Group II.—Surgery, Midwifery, and Diseases of Women.

I. R. Cook.

October.

Obtained Honours.

R. W. Allen (a)		P. S. Mills (d)
A. B. O'Brien (d, e).		

(a) Distinguished in Medicine.

(d) Distinguished in Surgery.

(e) Distinguished in Midwifery and Diseases of Women.

Pass.

E. Bellingham Smith.		E. C. Lowe.		H. A. Watney.
E. M. Harrison.		E. F. Milton.		W. Welchman.
A. G. Jones.		F. A. Sharpe.		T. F. Wilson.

Supplementary Pass List.

Group I.—Medicine, Pathology, and Forensic Medicine.

J. H. Horton.		T. C. Pocock.
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Group II.—Surgery, Midwifery, and Diseases of Women.

T. H. Barton.		G. Hamilton.		T. Turner.
R. J. Bentley.		H. S. Knight.		

General Intermediate Examination in Medicine.

January.

S. H. Cummings Air.		E. L. W. Mandel.		M. J. Rattray.
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July.

L. T. Baker.		W. Johnson.		J. T. Smalley.
H. B. Carter.		E. L. M. Lobb.		St. J. A. M. Tolhurst.
A. F. W. Denning.		H. E. Perkins.		V. Townrow.
R. C. V. Edsall.		H. A. Sanford.		

Special Examination in Organic Chemistry only.

January.

H. O. Brookhouse.		J. A. Bullbrook.		A. E. Lees.
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July.

J. Pryce Davies.		G. F. Haycraft.		G. H. Peall.
E. L. Elliott.		J. L. Johnstone.		J. R. Perdrau.
A. L. Fitzmaurice.		T. Lewis Jones.		N. A. D. Sharp.

Preliminary Scientific Examination.

January.

Inorganic Chemistry, Experimental Physics, and Biology.

J. Lee Atkinson.*

Inorganic Chemistry and Experimental Physics.

G. B. Cockrem.		A. L. Fitzmaurice.*
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Inorganic Chemistry and Biology.

E. A. Penny.*

Experimental Physics and Biology.

W. H. Talfourd Jones.		T. T. O'Callaghan.
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Inorganic Chemistry only.

H. Archer.		G. F. Haycraft.*		G. H. Peall.*
C. H. Crump.*		P. Hirschbein.*		J. R. Perdrau.*
J. Pryce Davies.*		J. L. Johnston.*		N. A. D. Sharp.*
E. L. Elliott.*		T. Lewis Jones.*		

Experimental Physics only.

D. A. Mitchell.		C. G. Morris.
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* Denotes completion of Examination.

July.

Inorganic Chemistry, Experimental Physics, and Biology.

R. P. Ballard.*		G. R. Hind.*		T. D. M. Stout.*
F. A. Dick.*		G. Maxted.*		A. D. Vazquez.*
G. Dunderdale.*		R. Rodgers.*		

Experimental Physics and Biology.

W. E. Fox.		G. T. Mullally.		R. Stout.
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Inorganic Chemistry only.

H. Davies.		*D. A. Mitchell.		*T. T. O'Callaghan.
		*C. Witts.		

Experimental Physics only.

J. A. Delmege.		A. G. H. Moore.		J. L. Stewart.
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Biology only.

E. A. Barker.		*G. B. Cockrem.		C. G. Morris.
		B. T. Verver.		

* Denotes completion of Examination.

Intermediate Examination in Science.

(Includes Preliminary Scientific Examination.)

*J. Lee Atkinson.		*W. H. Catto.		*E. M. A. Duvivier.
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University of Durham.

Examination for the Degree of Doctor in Medicine.

G. Burton-Brown. | J. G. O. H. Lane. | A. A. Miller.

*Examination for the Degree of Doctor in Medicine for Practitioners
of Fifteen Years' Standing.*

J. A. Ward.

Examination for the Degree of Master in Surgery.

J. G. O. H. Lane.

*Final Examination for the Degrees of Bachelor of Medicine
and Bachelor of Surgery.*

B. W. Lacey. | A. V. Maybury. | A. A. Smith.

*Third Examination for the Degrees of Bachelor of Medicine
and Bachelor of Surgery.*

E. P. H. Joynt. | H. F. Joynt.

*Second Examination for the Degrees of Bachelor of Medicine
and Bachelor of Surgery.*

E. P. L. Hughes.

University of Brussels.

Examination for the Degree of Doctor in Medicine.

E. G. Andrews.

Royal College of Physicians of London.

Elected to the Fellowship.

J. W. Russell, M.D. | E. Ivens Sprigg, M.D.

Examination for the Membership.

J. G. Harsant, M.D. | A. F. Hertz, M.B. | W. M. Robson, M.D.

Final Examination for the License.

January.

R. D. Bridger.	C. P. Harvey.	A. Morris.
A. D. Crofts.	A. V. Maybury.	S. M. Wells.

April.

H. C. Cameron.	E. N. Jupp.	D. H. Richards.
G. H. Cheyney.	B. W. Lacey.	J. D. Thomas.
C. J. S. Dismorr.	P. F. Minett.	
G. F. Hardy.	A. B. O'Brien.	

July.

J. E. Collins.	A. G. Jones.	T. C. Pocock.
H. P. Costobadie.	H. S. Knight.	H. A. Watney.
L. G. Davies.	R. P. Lewis.	W. Welchman.
R. Edridge.	A. H. Miller.	
G. Hamilton.	G. H. Morris.	

October.

J. M. Barrionuevo.	F. D. Crew.	G. H. K. Macalister.
L. H. Burner.	G. F. Greening.	P. S. Mills.
H. J. Clarke.	E. M. Harrison.	W. Reeve.
G. Cockcroft.	H. M. Langdale.	J. E. Scales.
V. A. P. Costobadie.	E. C. Lowe.	M. Bramley Taylor.

Royal College of Surgeons of Edinburgh.

Examination for the Fellowship.

F. C. Hitchens.	C. P. Weekes.
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Royal College of Surgeons of England.

Final Examination for the Fellowship.

Major E. M. Pilcher, R.A.M.C.	O. W. Richards.
C. D. Pye-Smith.	G. B. Thomson.

First Examination for the Fellowship.

E. C. Bevers.	C. W. Greene.	H. A. Sanford.
K. H. Digby.	R. A. Greeves.	G. F. Symes.

Final Examination for the Membership.

January.

R. D. Bridger.	C. P. Harvey.	A. Morris.
A. D. Crofts.	A. V. Maybury.	S. M. Wells.

April.

H. C. Cameron.	G. F. Hardy.	A. B. O'Brien.
G. H. Cheyney.	E. N. Jupp.	D. H. Richards.
C. J. S. Dismorr.	P. F. Minett.	J. D. Thomas.
	B. W. Lacey.	

July.

J. E. Collins.	A. G. Jones.	T. C. Pocock.
H. P. Costobadie.	H. S. Knight.	H. A. Watney.
L. G. Davies.	R. P. Lewis.	W. Welchman.
R. Edridge.	A. H. Miller.	
G. Hamilton.	G. H. Morris.	

October.

J. M. Barrionuevo.	F. D. Crew.	G. H. K. Macalister.
L. H. Burner.	G. F. Greening.	P. S. Mills.
H. J. Clarke.	E. M. Harrison.	W. Reeve.
G. Cockcroft.	H. M. Langdale.	J. E. Scales.
V. A. P. Costobadie.	E. C. Lowe.	M. B. Taylor.

Examination for the Diploma in Public Health.

Staff-Surgeon A. R. Bankart, R.N., M.V.O.	J. A. Glover.
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Society of Apothecaries of London.

H. R. Grellet.	R. H. Terry.	E. W. A. Walker.
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Royal Army Medical Corps.

G. B. F. Churchill.	R. P. Lewis.	G. H. Rees.
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Indian Medical Service.

O. H. Reinhold.

THE PHYSICAL SOCIETY.

Honorary President.—Sir Samuel Wilks, Bart., M.D., LL.D., F.R.S.

Honorary Vice-Presidents.—Sir Henry Howse, M.S., J. F. Goodhart, M.D., LL.D., P. H. Pye-Smith, B.A., M.D., F.R.S., G. H. Savage, M.D.

Secretaries.—

Presidents.—H. C. Cameron, M.A., B.C., J. S. Cooper, M.A., M.B., B.C., K. H. Digby, G. H. K. Macalister, B.A., M.B., B.C., C. W. Greene, B.A., G. W. Goodhart, B.A., H. S. Knight, P. P. Laidlaw, C. F. L. Leipoldt.

Session, 1905-6.—The Treasurer's Prize of £5 was awarded to Mr. G. H. K. Macalister for his paper on "The Prognostic Significance of Purpura in Children."

The Society's Prize was divided: to Mr. G. W. de P. Nicholson for his paper, "Tumours of the Testicle," £7, and to Mr. C. L. Leipoldt, £3, for his paper on "Suppurative Pylephlebitis."

CLINICAL APPOINTMENTS HELD DURING THE YEAR, 1905.

HOUSE PHYSICIANS.

A. F. Hertz
C. E. Iredell
O. V. Payne

G. A. Ticehurst
J. H. Clatworthy
R. A. Chisolm

F. Alcock
F. W. Morton Palmer

HOUSE SURGEONS.

M. G. Louisson
G. C. F. Robinson (3 mo)
E. W. Sheaf

Wm. Mollison
H. C. C. Mann (3 mo)
A. Leeming

P. P. Cole
E. C. Hughes
S. M. Wells

OUT-PATIENT OFFICERS.

F. Alcock
G. C. F. Robinson
F. W. Morton Palmer
A. Leeming
H. M. Clarke
R. O. Williams

P. P. Cole
J. H. Clatworthy
E. W. Sheaf
O. V. Payne
W. N. May

C. E. Iredell
E. C. Hughes
R. A. Chisolm
S. M. Wells.
A. B. O'Brien

ASSISTANT HOUSE SURGEONS.

H. H. Carter
M. Mottram
W. T. Meade-King
H. M. Clarke
L. G. Davies
H. M. Woodward

W. N. May
R. Felton
F. J. H. Wood
R. E. French
H. C. Cameron

G. W. Russell
O. V. Payne
A. B. O'Brien
C. M. Stevenson
A. D. Crofts

OBSTETRIC RESIDENTS.

F. P. Hughes	J. S. Cooper	N. I. Spriggs
H. H. Carter	L. S. H. Glanville	A. M. Webber
F. T. H. Wood	G. A. Ticehurst	

CLINICAL ASSISTANTS.

E. C. Hughes	R. Felton	W. N. May
W. T. P. Meade-King	F. W. Morton Palmer	E. W. Sheaf
A. V. Maybury	R. A. Chisolm	H. M. Clarke
A. Leeming	S. M. Wells	A. B. O'Brien
H. C. Cameron	A. D. Crofts	R. E. French
F. Rogerson	G. W. Russell	R. O. Williams
C. M. Stevenson	R. Edridge	A. G. Jones
A. H. Miller	W. Reeve	H. D. Wyatt

CLINICAL ASSISTANTS IN THE MEDICAL WARDS.

W. Reeve	G. Hamilton	H. S. Knight
F. D. Crew	R. Edridge	E. Bellingham Smith
C. F. Fothergill	G. W. Nicholson	W. H. S. Burney
A. S. M. Palmer	W. Welchman	J. S. Bookless
G. H. K. Macalister	W. P. Purdom	M. Leckie
E. L. Norton		

CLINICAL ASSISTANTS IN THE SURGICAL WARDS.

G. F. Hardy	W. P. Purdom	G. H. K. Macalister
F. H. T. Wood	T. C. Pocock	E. F. Milton
H. A. Watney	T. F. Wilson	H. M. Langdale
T. Norman	H. G. Gibson	R. Davies-Colley

SURGEONS' DRESSERS.

J. S. Bookless	C. H. Marshall	H. F. Joynt
I. Valerio	W. H. Robinson	A. Shepperd
T. H. Barton	Patterson-Clavier	R. Willan
E. L. R. Norton	A. W. Berry	W. H. Trethowan
G. Wachter	J. G. Phillips	A. Walker
R. Davies-Colley	A. S. B. Bankart	C. M. Ockwell
E. M. Harrison	G. W. Goodhart	H. H. Moyle
H. J. Clarke	E. C. Lowe	F. A. Barker
E. Morgan	G. Cockcroft	P. D. Magowan
J. S. Farnfield	E. H. Paterson	G. R. Phillips
J. E. Hodson	W. H. Miller	G. N. Bartlett
A. Alcock	H. E. H. Tracy	C. F. L. Leipoldt
C. W. Greene	T. B. Layton	H. C. Malleson
H. A. Pallant	A. Zorab	H. E. B. Walling
P. F. McEvedy	S. K. Poole	O. G. F. Luhn
J. T. Smalley	G. F. E. Allison	M. M. Earle
A. T. Rivers	E. Wragg	B. K. Nutman
J. L. Rankine	C. E. M. Jones	W. R. Greening
A. Davidson	S. W. Daw	H. J. Henderson
T. E. A. Carr	C. A. L. Mayer	J. N. Watson
B. Wallis	G. W. Dryland	R. J. Reynolds
St. J. A. Tolhurst	E. P. H. Joynt	P. P. Laidlaw
W. P. H. Munden	E. W. Giesen	G. F. Stebbing
G. A. Ticehurst	S. McK. Saunders	E. B. Hinde
H. J. Smith	C. A. Basker	

ASSISTANT SURGEONS' DRESSERS.

M. M. Earle	A. Davidson	C. E. M. Jones
A. T. Rivers	B. K. Nutman	G. F. E. Allison
F. Wragg	S. W. Daw	O. G. F. Luhn
S. K. Poole	J. T. Smalley	C. H. Marshall
G. W. Dryland	P. P. Laidlaw	W. P. H. Munden
S. McK. Saunders	G. F. Stebbing	E. B. Hinde
J. B. Ball	C. B. Ticehurst	T. E. A. Carr
E. W. Giesen	R. J. Reynolds	H. J. Henderson
H. P. Aubrey	J. N. Watson	C. A. Basker
J. A. Tolhurst	E. N. Plummer	H. F. Joynt
C. P. Joynt	C. A. L. Mayer	E. P. Minett
H. J. Smith	B. Wallis	H. B. Carlyll
J. A. K. Helm	A. V. Ledger	A. T. Densham
R. Evans	L. D. Stamp	R. B. Dawson
N. Flower	A. L. Foster	T. N. Wood
R. R. Walker	J. W. Grice	C. H. Rippmann
H. J. B. Cane	F. Morris	G. G. Timpson
T. H. Edey	J. D. Featherstone	L. L. C. Reynolds
M. D. Price	K. H. Digby	M. R. Dobson
H. S. C. Air	C. D. Roberts	L. Croft
M. J. Rattray	J. B. Martin	W. W. Cook
A. C. Dickson	B. H. Palmer	I. R. Florence
E. A. Collins	P. F. McEvedy	

DENTAL SURGEONS' DRESSERS.

V. A. P. Costobadie	A. H. Clough	O. V. Payne
R. J. Bentley	J. H. Mayston	F. B. Lowe
E. M. Harrison	E. C. Lowe	H. D. Wyatt
F. D. Crew	B. B. Metcalfe	

CLINICAL ASSISTANTS IN MEDICAL OUT-PATIENTS.

C. M. Wenyon	W. P. Purdom	A. G. Jones
M. Leckie	C. M. Ockwell	H. G. Gibson
J. H. Mayston	W. H. Miller	

OPHTHALMIC DRESSERS.

C. M. Stevenson	A. B. O'Brien	S. M. Wells
A. M. Webber	G. H. K. Macalister	J. Barrionuevo
J. E. Scales	A. H. Miller	H. D. Wyatt
G. Hamilton	C. W. Ponder	F. D. Crew
H. V. Mitchell	F. A. Sharpe	H. S. Knight
W. P. Purdom	A. Walker	L. G. Davies
C. F. Fothergill	J. S. Farnfield	G. Wachter
J. H. Mayston	G. W. Nicholson	H. E. H. Tracy
P. S. Mills	A. W. Berry	E. H. Adams
H. J. Clarke	W. H. S. Burney	I. Valerio

DRESSERS IN THE THROAT DEPARTMENT.

H. C. Cameron	R. E. French	D. Isaacs
V. A. P. Costobadie	C. M. Stevenson	F. Rogerson
E. H. Adams	W. Reeve	E. B. Smith
F. T. H. Wood	H. V. Mitchell	G. W. Nicholson
A. S. B. Bankart	L. G. Davies	G. Hamilton
H. S. Knight	G. H. K. Macalister	A. H. Miller
W. H. S. Burney	F. D. Crew	E. M. Harrison
E. C. Lowe	B. B. Metcalfe	A. S. M. Palmer

CLERKS IN THE SKIN DEPARTMENT.

W. P. Purdom	C. H. Rippmann	W. H. S. Burney
S. W. Daw	T. B. Layton	J. S. Bookless
	C. M. Ockwell	

AURAL SURGEONS' DRESSERS.

F. M. Longson	O. V. Payne	A. R. Wilson
L. G. Davies	H. V. Mitchell	H. S. Harper
G. H. K. Macalister	A. S. B. Bankart	W. P. Purdom
W. H. Trethowan	G. Cockcroft	E. Alban

MEDICAL WARD CLERKS.

J. W. Featherstone	T. H. Edey	R. B. Dawson
J. E. Hodson	St. A. M. Tolhurst	T. B. Layton
E. Morgan	A. Zorab	E. W. Giesen
H. C. Malleston	W. H. Miller	W. P. H. Munden
H. A. Pallant	E. N. Plummer	R. J. Reynolds
S. McK. Saunders	C. F. Stebbing	H. E. H. Tracy
J. S. Farnfield	E. P. H. Joynt	H. F. Joynt
C. F. L. Leipoldt	H. J. Smith	J. N. Watson
A. Alcock	P. P. Laidlaw	C. B. Ticehurst
T. N. Wood	J. B. Ball	E. B. Hinde
H. P. Aubrey	C. A. Basker	T. E. A. Carr
H. J. Henderson	C. H. Marshall	C. A. L. Mayer
G. W. Dryland	B. Wallis	S. K. Poole
P. F. McEvedy	S. W. Daw	A. T. Rivers
G. F. E. Allison	E. Wragg	A. Davidson
M. M. Earle	J. L. Rankine	W. R. Greening
C. E. M. Jones	B. K. Nutman	O. G. F. Luhn
J. K. A. Helm	I. R. Florence	A. V. Ledger
F. Morres	L. D. Stamp	A. L. Foster
M. D. Price	C. H. Rippman	H. J. B. Cane
N. Flower	H. B. Carlyll	A. T. Densham
R. Evans	J. W. Grice	A. C. Dickson
R. R. Walker	E. A. Collins	J. T. Smalley
B. Wallis	K. H. Digby	C. B. Ticehurst
L. L. C. Reynolds	S. H. C. Air	M. J. Rattray
L. Croft	A. N. Leeming	W. W. Cook
C. D. Roberts	B. H. Palmer	J. B. Martin
P. K. Taraporwala	L. D. Stamp	M. R. Dobson
N. P. Pinching	A. H. V. St. John	F. H. Fuller
C. E. Price	M. K. Nelson	H. E. Perkins
G. G. Timpson	A. F. W. Denning	J. H. Ryffel

ASSISTANT PHYSICIANS' CLERKS.

H. W. B. Walling	E. H. Paterson	G. R. Phillips
E. P. Minett		

SURGICAL WARD CLERKS.

T. H. Edey	E. A. Collins	R. B. Dawson
A. V. Ledger	F. Morris	J. K. A. Helm
A. L. Foster	M. D. Price	C. H. Rippmann
N. Flower	J. W. Featherstone	H. B. Carlyll
A. T. Densham	H. J. B. Cane	R. R. Walker
R. Evans	J. W. Grice	A. C. Dickson
I. R. Florence	L. D. Stamp	K. H. Digby
F. W. Hogarth	P. V. G. Pedrick	M. J. Rattray
D. Reynolds	L. L. C. Reynolds	J. B. Martin
G. F. Syms	S. H. C. Air	W. W. Cook
L. Croft	C. D. Roberts	B. H. Palmer
A. N. Leeming	M. R. Dobson	M. K. Nelson
F. W. Hogarth	H. E. Perkins	M. E. Ball
C. D. Plumptre	W. G. Pinching	A. H. St. John
C. E. Price	A. F. W. Denning	R. C. F. Edsall
W. Johnson	L. T. Baker	H. B. Carter
E. R. Stone	J. F. Young	H. Stott
W. Edmeades	T. Evans	H. E. Lucey
L. T. Dean	C. E. Douglas	R. G. Chase
R. P. M. Roberts	A. W. Ewing	H. Chapple
C. H. Mills		

ASSISTANT SURGEONS' CLERKS.

K. H. Digby	S. H. C. Air	H. E. H. Tracy
M. J. Rattray	C. D. Roberts	B. H. Palmer
C. F. L. Leipoldt	J. B. Martin	H. E. Perkins
C. M. Plumptre	M. E. Ball	W. W. Cook
A. Samuel	E. P. Minett	A. V. H. St. John
F. W. Hogarth	C. E. Price	

POST-MORTEM CLERKS.

A. H. Miller	A. Alcock	C. W. Greene
F. A. Sharp	G. W. Nicholson	E. H. Adams
R. H. Bentley	E. B. Smith	C. F. Fothergill
R. S. Harper	E. F. Milton	B. B. Metcalfe
P. S. Mills	H. A. Watney	A. S. M. Palmer
A. W. Berry	H. F. Vandermin	O. F. G. Luhn
W. P. Purdom	A. Walker	E. C. Lowe
E. Cockcroft	E. M. Harrison	W. H. Trethowan
J. S. Bookless	W. Welchman	T. H. Barton
A. G. Jones	L. Norton	E. Alban
C. C. De Villiers	T. F. Wilson	C. M. Ockwell
P. D. Magowan	J. G. Phillips	J. E. Hodson
N. Flower	M. Leckie	R. Davies-Colley
G. W. Goodhart	R. Evans	G. N. Bartlett
A. S. B. Bankart	T. B. Layton	W. H. Miller
	F. A. Barker	

OBSTETRIC DRESSERS.

R. Edridge	T. C. Pocock	F. T. H. Wood
H. V. Mitchell	A. B. O'Brien	W. P. Purdom
A. G. Jones	W. Welchman	J. H. Mayston
S. Reader	H. G. Gibson	H. C. Cameron
H. S. Knight	W. H. S. Burney	I. R. Cook
W. Reeve	E. H. Adams	E. B. Smith
R. J. Bentley	I. Valerio	H. F. Vandermin
P. S. Mills	G. W. Nicholson	E. M. Harrison
E. C. Lowe	T. H. Barton	L. H. Norton
A. W. Berry	F. J. J. Orpen	J. S. Bookless
G. Cockcroft	C. M. Ockwell	C. C. De Villiers
H. C. Malleston	W. H. Trethowan	

EXTERN OBSTETRIC ATTENDANTS.

R. J. Bentley	H. A. Watney	J. H. Mayston
E. F. Fothergill	E. F. Milton	P. D. Magowan
A. G. Jones	W. Welchman	H. G. Gibson
G. H. Morris	T. F. Wilson	F. C. Litchfield
T. C. Pocock	A. S. M. Palmer	W. H. S. Burney
H. F. Vandermin	P. S. Mills	E. Alban
H. C. Malleson	C. C. De Villiers	H. E. H. Tracy
J. S. Farnfield	H. A. Pallant	A. S. B. Bankart
G. Wachar	E. C. Lowe	E. M. Harrison
I. Valerio	L. J. Patterson-Clavier	J. G. Phillips
P. F. McEvedy	H. J. Clarke	A. W. Berry
W. H. Robinson	J. T. Smalley	E. L. R. Norton
T. B. Layton	T. H. Barton	E. Morgan
R. Davies-Colley	G. W. Goodhart	G. Cockcroft
W. H. Trethowan	C. W. Ponder	F. A. Barker
H. Moyle	T. E. A. Carr	C. M. Ockwell
G. F. Stebbing	G. R. Phillips	P. K. Taraporwala
A. Zorab	G. F. E. Allison	M. M. Earle
C. E. M. Jones	A. T. Rivers	E. H. Paterson
O. G. F. Luhn	C. W. Greene	E. P. Minett
R. Willan		

CLERKS TO ANÆSTHETISTS.

G. H. K. Macalister	C. F. Fothergill	R. M. Wingent
R. Edridge	M. Leckie	T. Norman.
G. W. Nicholson	A. W. Eyles	W. P. Purdom
A. Walker	W. H. S. Burney	C. C. De Villiers
B. B. Metcalfe	E. H. Adams	T. F. Wilson
R. S. Harper	J. H. Mayston	E. F. Milton
J. G. Phillips	S. Reader	L. H. Burner
H. J. Clarke	H. F. Vandermin	L. J. Patterson-Clavier
A. G. Jones	G. Cockcroft	P. C. Litchfield
P. D. Magowan	G. H. Rees	E. Morgan
E. M. Harrison	H. G. Gibson	E. L. R. Norton
W. Welchman	E. C. Lowe	P. S. Mills
R. J. Bentley	H. C. Cameron	S. M. Palmer
W. H. Trethowan	A. W. Berry	J. A. C. Greene
E. Alban	T. C. Pocock	T. H. Barton
T. G. Scott	C. W. Ponder	W. R. Greening
H. B. Walling	E. B. Smith	J. S. Bookless
H. M. Wingent	T. B. Layton	A. Shepperd
F. A. Barker	J. S. Farnfield	G. Wachar
I. Valerio	A. M. Roome	J. L. Rankine
I. R. Florence	H. J. Smith	G. N. Bartlett
M. M. Earle	C. A. L. Meyer	W. H. Robinson
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P. K. Taraporwala	G. W. Goodhart	E. P. Minett
A. Zorab	R. Willan	E. H. Paterson
H. H. Moyle	O. G. F. Luhn	M. D. Price
C. E. M. Jones	J. E. Hodson	H. E. H. Tracy
H. A. Pallant	C. W. Greene	A. S. B. Bankart
A. Alcock		

DENTAL SCHOOL

APPOINTMENTS HELD DURING THE YEAR 1905.

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J. W. Mawer	F. S. Vine	J. B. Ball
	A. Alan Forty	

ASSISTANT HOUSE SURGEONS.

A. Alan Forty	H. Snell	F. H. Fuller
A. W. Parrott	J. A. Bowes	J. McBride
S. G. Elliott	C. E. Lloyd	

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J. A. Bowes	F. J. Messer	J. McBride
S. G. Elliott	C. Weller	C. E. Lloyd
F. M. Holborn	H. E. Marsh	H. Simms

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E. S. Pierrepont	W. E. Freeman	W. J. P. Dicks
S. G. Elliott	C. E. Lloyd	R. P. Fenn
H. E. Marsh	D. G. Wearing	P. V. G. Pedrick
W. E. Cook	F. J. Cutler	J. McBride
O. J. Roots	N. P. Rodgers	C. Weller
C. M. Craig	A. E. Webb	W. H. Plowman
B. B. Samuel	F. M. Holborn	H. L. Power
E. D. R. Jacob	H. J. Weighell	F. J. Messer
G. E. Rice	C. C. Freer	G. Warren
J. R. D. Ditch	C. G. G. Lewis	H. V. Sharp
H. G. Clark	H. T. Reeve	W. E. Freeman
W. T. Dean	O. B. Townshend	H. G. Dumayne
T. L. Smith	H. L. Power	E. L. Brown
N. V. H. Riches	E. N. Plummer	H. Simms
A. H. Pickett	R. R. B. Ponder	G. L. Davies
I. Margolies	W. S. Rutter	

DRESSERS IN THE EXTRACTION ROOM.

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C. G. G. Lewis	F. M. Holborn	V. Masters
W. S. Rutter	J. R. D. Ditch	R. J. Oliver
H. T. Genge	R. R. B. Ponder	G. L. Davies
I. Margolies	H. J. Weighell	E. Barnett
R. Redpath	F. Giles	E. D. R. Jacob
H. Simms	A. E. Webb	H. T. Reeve
G. Warren	G. L. Davies	H. O. Salt
H. G. Clark	J. E. Hanna	H. E. Marsh
H. G. Dumayne	W. H. Plowman	H. S. Robins
W. G. Oliver	H. J. Dear	A. H. Gabell
W. T. Boxall		

DRESSERS IN THE CONSERVATION ROOM.

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F. H. Fuller	F. M. Holborn	G. Packham
A. W. Parrott	T. Scott-Foster	H. Snell
W. J. C. Timberlake	G. G. Timpson	R. G. H. Warner
P. V. G. Pedrick	J. McBride	J. A. Bowes
C. M. Craig	W. J. P. Dicks	H. G. Dumayne
R. P. Fenn	W. E. Freeman	E. S. Pierrepont
H. E. Alexander	R. Beadnell-Gill	C. G. G. Lewis
H. T. Reeve	C. R. Rudolf	A. E. Webb
F. L. Aubrey	W. E. Cook	W. T. Dean
E. D. R. Jacob	F. G. Gillett	F. J. Messer
C. L. Pemberton	G. E. Rice	O. J. Roots
H. Simms	H. J. Weighell	H. G. Clark
A. A. Forty	C. C. Freer	O. G. Iliffe
B. B. Samuel	F. A. Beckley	W. Elwood
W. H. Helyar	H. G. Pearce	W. H. Plowman
T. L. Smith	A. S. Thomas	D. G. Wearing
C. Weller	L. B. Moore	N. P. Rodgers
E. L. Brown	S. G. Elliott	R. A. Glindon
C. E. Lloyd	H. E. Marsh	H. L. Power
H. V. Sharp	G. Warren	B. L. Weaver
P. F. Minett	H. T. Genge	R. Redpath

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V. Masters	W. T. Clarke	R. Redpath
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J. R. D. Ditch	W. S. Rutter	F. Giles
I. Margolies	H. T. Genge	A. H. Pickett
H. O. Salt	R. J. Oliver	D. Y. Hylton
H. J. Dear	W. T. Clarke	W. F. Boxall
W. G. Oliver.	A. H. Gabell	

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F. M. Holborn	H. T. Reeve	N. P. Rodgers
H. G. Clark	H. L. Power	G. Warren
R. Beadnell-Gill	H. V. Sharp	H. Simms
R. A. Glindon	E. L. Brown	C. C. Freer
J. R. D. Ditch	I. Margolies	H. G. Dumayne
C. G. G. Lewis	V. Masters	G. Packham
G. L. Davies	A. H. Pickett	O. G. Iliffe
N. V. H. Riches	W. S. Rutter	R. R. B. Ponder
J. E. Hanna	R. J. Oliver	W. T. Clarke
C. E. Lloyd		

GUY'S HOSPITAL.

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Consulting Physician for Mental Diseases.—G. H. SAVAGE, M.D.

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Consulting Aural Surgeon.—W. LAIDLAW PURVES, M.D.

Consulting Anæsthetist.—TOM BIRD, Esq.

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G. NEWTON PITT, M.D.

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L. E. SHAW, M.D.

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Physician for Mental Diseases.

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Physician in Charge of Skin Department.

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Obstetric Registrar and Tutor.

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Surgeon in Charge of Aural Department.

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J. L. PAYNE, Esq.

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<i>Clinical Medicine</i>	THE PHYSICIANS & ASSISTANT PHYSICIANS
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(Lectures)	HALE WHITE, M.D.
<i>Practical Medicine</i>	H. F. BELL WALKER, M.D., AND
	H. C. C. MANN, M.D.
<i>Medical Revision Classes</i>	H. S. FRENCH, M.D.

Surgery.

<i>Clinical Surgery</i>	THE SURGEONS AND ASSISTANT SURGEONS
<i>Principles and Practice of Surgery</i>	CHARTERS J. SYMONDS, M.S., W.
(Lectures)	ARBUTHNOT LANE, M.S., AND L.
	A. DUNN, M.S.
<i>Operative Surgery</i>	C. H. FAGGE, M.S., R. P. ROWLANDS, M.S.
	Demonstrator, P. TURNER, M.S.
<i>Practical Surgery</i>	R. A. GREEVES, M.B., B.S.
<i>Surgical Revision Classes</i>	C. H. FAGGE, M.S.

Obstetrics and Gynaecology.

<i>Clinical Gynaecology</i>	THE OBSTETRIC PHYSICIANS AND
	ASSISTANT OBSTETRIC PHYSICIANS.
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	TARGETT, M.S.
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<i>Obstetric Revision Classes</i>	G. BELLINGHAM SMITH, M.B., B.S.

Pathology.

<i>Pathology</i> (Lectures)	GEORGE NEWTON PITT, M.D., AND
	F. W. BAINBRIDGE, M.D., D.Sc.
	(Gordon Lecturer).
<i>Morbid Anatomy</i> (Demonstrations	J. FAWCETT, M.D., AND H. S.
in Post-mortem Room)	FRENCH, M.D.
<i>Surgical Pathology</i> (Demonstrations)	R. P. ROWLANDS, M.S.
<i>Medical Pathology</i> (Demonstrations)	J. FAWCETT, M.D.
<i>General Pathology</i> (Demonstrations)	A. P. BEDDARD, M.D.
<i>Morbid Histology</i>	G. BELLINGHAM SMITH, M.B., B.S.

Ophthalmology.

<i>Clinical Ophthalmology</i>	THE OPHTHALMIC SURGEONS.
<i>Ophthalmology</i> (Lectures)	H. L. EASON, M.S., M.D.

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J. F. SYKES, M.D.

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J. W. H. EYRE, M.D.

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B.Sc.**Physics.***Physics* (Lectures) ... A. H. FISON, D.Sc.*Practical Physics* ... R. W. MERRIMAN, B.Sc.**Biology.***Biology* (Lectures) ... RICHARD ASSHETON, M.A.*Practical Biology* ... T. G. STEVENS, M.D., AND A. R.
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M. S. PEMBREY, M.D. (Oxon.).*Special Tutors for Cambridge Men* SIR E. COOPER PERRY, M.D. (Cantab.),
AND W. M. MOLLISON, M.B.,
M.C. (Cantab.).

The Hospital contains accommodation for 602 Patients, an additional 50 Beds having been opened on the Medical side of the Hospital.

Special Classes are held for Students preparing for the University and other Higher Examinations.

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All Hospital Appointments are made strictly in accordance with the merits of the Candidates, and without extra payment. There are 24 Resident Appointments open to Students of the Hospital annually without payment of additional fees, and numerous Non-resident Appointments in the general and special departments. The Queen Victoria Ward provides accommodation for gynaecological and maternity cases.

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Two Open Scholarships in Arts, one of the value of £100 open to Candidates under 20 years of age, and one of £50 open to Candidates under 25 years of age. Two Open Scholarships in Science, one of the value of £150, and another of £60, open to Candidates under 25 years of age. One Open Scholarship for University Students who have completed their study of Anatomy and Physiology, of the value of £50.

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Are awarded to Students in their various years, amounting in the aggregate to more than £650.

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The Residential College accommodates about 50 Students in addition to the Resident Staff of the Hospital. It contains a large Dining Hall, Reading Room, Library, and Gymnasium for the use of the Students' Club.

For Prospectus and further information, apply to the Dean, Dr. EASON, Guy's Hospital, London Bridge, S.E.

THE STAFF OF THE DENTAL SCHOOL. 1906.

Dental Surgeons.

F. NEWLAND-PEDLEY, F.R.C.S., L.D.S.E.
W. A. MAGGS, L.R.C.P., M.R.C.S., L.D.S.E.
R. WYNNE ROUW, L.R.C.P., M.R.C.S., L.D.S.E.

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M. F. HOPSON, L.D.S.E.	L.D.S.E.
	J. L. PAYNE, L.R.C.P., M.R.C.S.,
	L.D.S.E.

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E. B. DOWSETT, L.R.C.P., M.R.C.S.,	F. J. PEABCE, L.D.S.E.
L.D.S.E.	J. E. SPILLER, L.D.S.E.
P. S. CAMPKIN, L.D.S.E.	H. P. AUBREY, L.D.S.E.

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H. F. LANCASTER, M.D.	P. TURNER, M.S., F.R.C.S.
C. J. OGLE, M.R.C.S.	H. T. HICKS, F.R.C.S.
W. M. MOLLISON, M.C., F.R.C.S.	A. R. THOMPSON, M.B., Ch.B.,
	F.R.C.S.

Lecturers.

Dental Anatomy and Physiology.—Mr. MAGGS.
Dental Surgery and Pathology.—Mr. WYNNE ROUW.
Operative Dental Surgery.—Mr. PARFITT.
Dental Mechanics.—Mr. PAYNE.
Practical Dental Mechanics.—Mr. PILLIN.
Dental Materia Medica.—A. P. BEDDARD, M.D.
Dental Bacteriology.—J. W. H. EYRE, M.D.
Dental Microscopy.—A. F. HERTZ, M.B., B.Ch. AND H. C.
CAMERON, M.B., B.C.
Dental Metallurgy.—J. WADE, D.Sc.
Practical Dental Metallurgy.—Mr. HOPSON.
Curators of Dental Museum.—Mr. PAYNE AND Mr. DOWSETT.
Dean.—Dr. EASON.

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4. A Case of Subdiaphragmatic and Hepatic Abscess Consecutive to Mediterranean Fever. By J. W. H. Eyre, M.D., and J. Fawcett, M.D.
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6. A Case of Severe Hæmocytolosis. By G. T. Wrench, M.B., and J. H. Bryant, M.D.
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List of Gentlemen Educated at Guy's Hospital who have passed the Examinations of the several Universities, Colleges, etc., in the year 1903.

Medallists and Prizemen for 1904.

The Physical Society.

Clinical Appointments held during the year 1903.

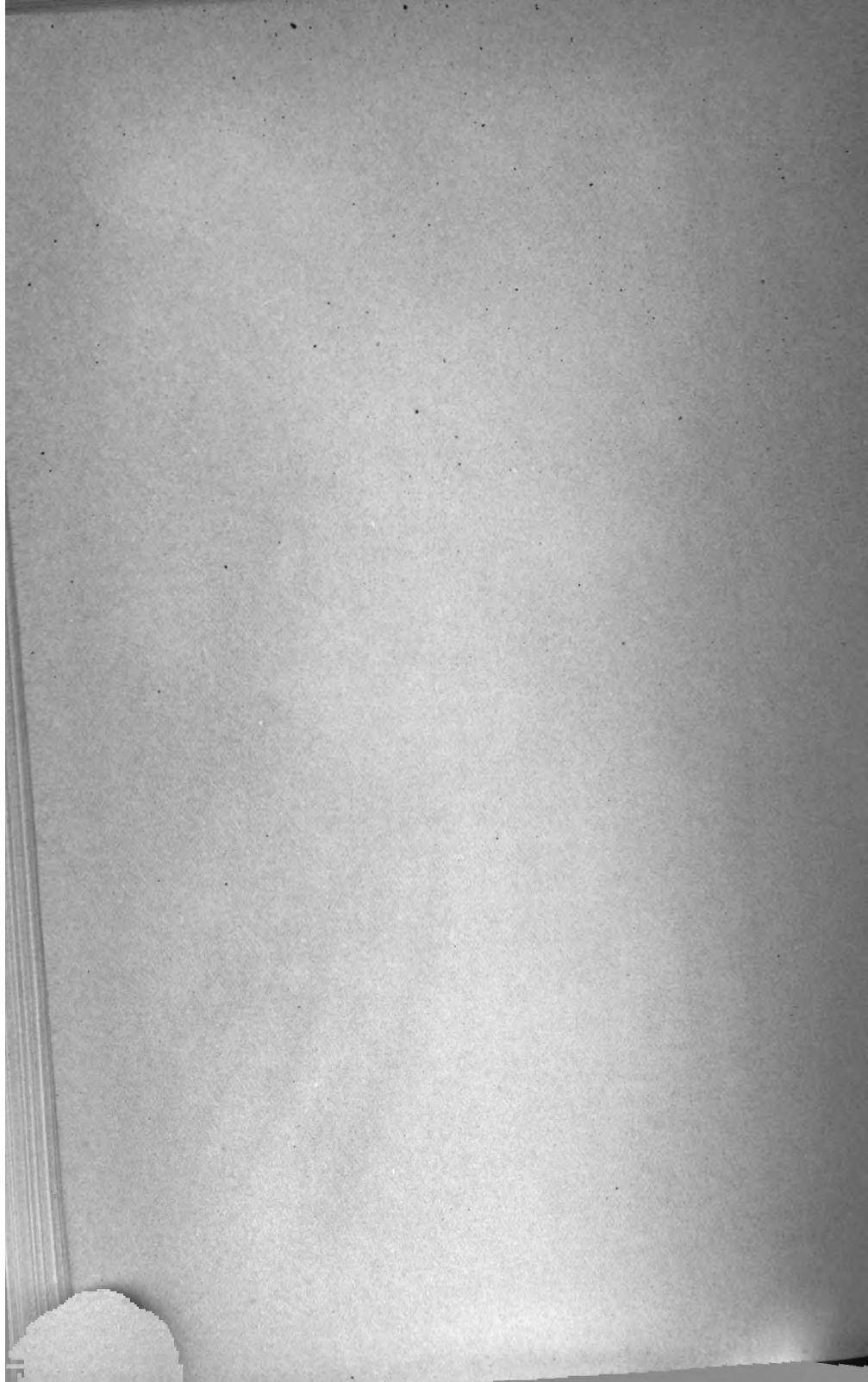
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Medical and Surgical Staff, 1904.

Lecturers and Demonstrators.

The Staff of the Dental School, 1904.

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Guy's Hospital reports.



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